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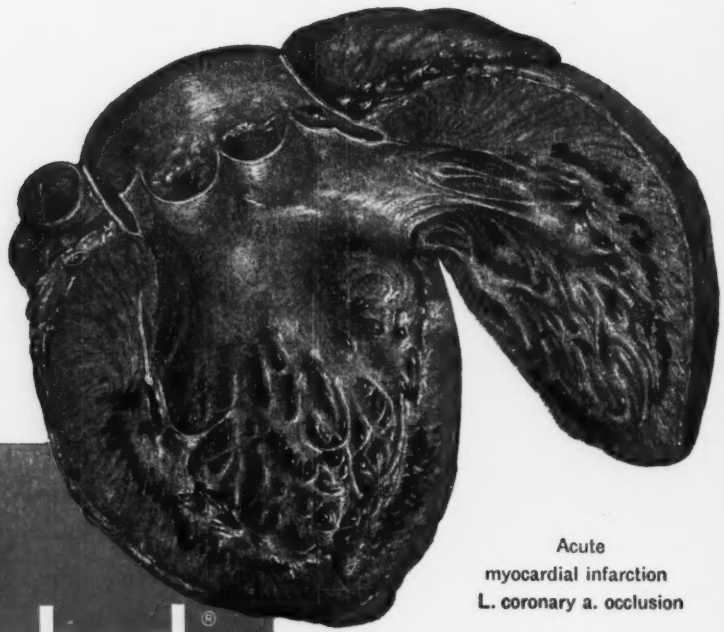
—in the severe shock

secondary to myocardial infarction



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1. Gazes, P. C., Goldberg, L. I., and Darby, T. D.: *Circulation*, 8: 883, Dec., 1953.

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T. Duckett Jones, 1899–1954

The country has lost a great pioneer in public health. The untimely death of T. Duckett Jones has deprived us of a leader who modestly but relentlessly pursued his goal of stimulating his medical colleagues and indeed the public at large to recognize the vital importance of putting to work and keeping at work "the best brains" in the country in medical research. Although his primary interests had been those of rheumatic fever and rheumatic heart disease and of child health in general, he enlarged his activity to embrace the entire field of cardiovascular disease and finally all aspects of public health and all the so-called basic sciences on which advances in our medical knowledge so largely depend. He was an indefatigable worker, constantly accepting invitations and requests to take part in so-called project-site visits to medical research groups all over the country, and often on his own, searching out workers, both young and older, to ascertain their suitability for research, their desires, and their needs. He had established himself in the hearts of hundreds of these workers as their counsellor and friend, and he brought to the meetings of his colleagues on councils, committees, and informal discussion groups, large or small, an account of his travels and sound advice. By his persistence and everlasting emphasis on the individual worker's ability and the need of its nurture in contrast to the traditionally established research project–grant system in vogue a decade ago he more than any other person, has helped to liberalize in the best sort of way both public and private support of medical research.

T. Duckett Jones was born in Petersburg, Virginia, in 1899, the son of Dr. Bolling Jones, who at one time in his own distinguished career served as President of the Virginia Medical Society. Of three sisters of T. Duckett Jones, one is a leading physician in Florida and the other two are wives of physicians. A brother is a surgeon.

Dr. Jones graduated in 1919 from the Virginia Military Institute and in medicine in 1923 from the University of Virginia, where he served his medical interneship and residency. In 1925 he came north and remained in Boston and New York City thereafter, first as Dalton Fellow and cardiac resident at the Massachusetts General Hospital, and, after a year as a National Research Council Fellow with Sir Thomas Lewis in London, he served as Director of Research in rheumatic fever and rheumatic heart disease at the House of the Good Samaritan in Boston for 20 years. During that period he served also on the faculty of the Harvard Medical School and on the staff of the Massachusetts General

Hospital. In 1947 he became Medical Director of the Helen Hay Whitney Foundation in New York City, whither he moved; this allowed freer scope to widen his interests in public health throughout the country.

In 1948 his usefulness in this cause was still further advanced by appointment to the first National Advisory Heart Council, which was established in that year along with the National Heart Institute by Act of Congress. It was in the deliberations of that Council especially that those of us who were fortunate enough to be fellow councillors with him relied so heavily on his experience and advice.

Other offices held by T. Duckett Jones were many and included Vice-Presidency of the American Heart Association, Chairmanship of that association's Council on Rheumatic Fever, and Presidency-elect of the National Health Council. But those of us who knew him best loved him as a loyal friend, modest, stimulating, and companionable. We shall sorely miss him.

Paul D. White, Executive Director,
National Advisory Heart Council.
Former President,
American Heart Association.

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Metabolic and Hemodynamic Changes Induced by the Prolonged Administration of Dextran

By JOHN R. JAENIKE, M.D., AND CHRISTINE WATERHOUSE, M.D.

Large amounts of dextran were administered to human subjects under standardized metabolic conditions, with the following results: Dextran is a potent osmotic substance which produces marked salt and water retention and rapid plasma volume expansion. About 50 per cent of the amount given is excreted in the urine during the injection period. Nitrogen and phosphorus sparing and an antiketogenic effect are produced during the period of administration. A fraction of the dextran remains circulating for a prolonged period of time and is associated with a sustained depression of venous hematocrit. Metabolism of this fraction cannot be demonstrated, and its ultimate fate in the body is unknown.

THE polysaccharide dextran has in recent years been the subject of intensive investigations, both in this country and abroad, because of its potentiality as a safe, effective, and readily available plasma expander. It has been subjected to extensive clinical trials,[1, 2] and numerous studies have attested to its ability to produce rapid and significant expansion of plasma volume, in both bled and normovolemic subjects.[3, 4] There is, however, little information concerning its long-term effects when infused into human subjects. In addition, although evidence exists that it is at least in part metabolized, its presence in the reticuloendothelial system has been observed, and it must be concluded that its ultimate fate in the body is unknown. The current use of large amounts of dextran therapeutically in such clinical states as the nephrotic syndrome emphasizes the practical importance of further defining the pharmacology of this agent.

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Dr. Jaenike is a Public Health Service Research Fellow of the National Heart Institute.

This investigation was supported by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service (H-1079).

The present study was set up for the purpose of determining the nature and duration of the hemodynamic and metabolic changes induced by dextran. In addition an attempt has been made to define quantitatively the ultimate fate of dextran, and to correlate this information with the observed hemodynamic and metabolic effects. Human subjects, showing no evidence of cardiovascular or metabolic disease, were selected for this purpose. Dextran* was administered in large amounts and relatively long-term observations were carried out.

PROCEDURES AND PATIENTS

The clinical background of the patients concerned in this study was as follows:

S.M., a Negro male, age 47, was admitted because of increasing dementia. A diagnosis of syphilis of the central nervous system with paresis was established. The process was considered inactive, and his clinical disease remained unchanged during the course of study.

W.W., a Negro male, age 38, and *J.J.*, a Negro male, age 43, had syphilis of the central nervous system with predominant meningovascular involve-

* The dextran used in this study was generously supplied by Commercial Solvents Corporation. Although several lots were administered, the molecular weights of various lots were relatively uniform Molecular weight ranged by 25,000 to 185,000 with an average of 70,000.

ment. Both were treated with penicillin and showed clearing of the acute process at the time of this study.

T.L., a white female, age 58, had a chronic stasis dermatitis with epidermophytosis and generalized id reaction. No other organic disease was in evidence.

G.D., a white male, age 23, was a patient with idiopathic epilepsy. He was otherwise clinically well. Two separate studies were performed on G.D., and will hereafter be designated as G.D. No. 1 and G.D. No. 2.

M.L., a white female, age 19, had a chronic neurodermatitis involving chiefly the head, ears, and perineal region. It was felt that psychogenic factors were of prime importance in her disease. The dermatitis was well controlled at the time this study was initiated.

R.T., a white male, age 21, was considered to have a psychopathic personality disorder. Despite a history of rheumatic fever, no definite evidence of residual cardiac damage was present, and there was otherwise no evidence of organic disease.

All subjects were admitted to a special metabolic division where well-controlled balance studies could be conducted. Diets were weighed and cooked under the supervision of the dietitian, and sample diets, duplicating in all respects the food served to the patients, were analyzed frequently throughout the course of the experiments.

Nitrogen, phosphorus, calcium, sodium, chloride, and potassium balances were carried out on all patients. Urine was collected in 24-hour periods, analyzed daily, and the results checked on pooled aliquots at the end of the metabolic periods. Stools were pooled into corresponding periods, separation being accomplished with carmine markers.

Each subject received a low caloric, low carbohydrate diet which induced ketosis in all, and negative nitrogen balance in all subjects but two (T.L. and M.L.).

A constant daily diet was given to five subjects, and two- and three-day rotating diets to S.M. and R.T., respectively. In the latter instance, the daily intake varied but slightly in composition.

Repeated dietary analyses revealed the following average daily intakes:

Sub.	N Gm.	P Gm.	Ca Gm.	Na mEq.	Cl mEq.	K mEq.	Calories
S.M.	10.55	.88	.328	172	171	52	1173
W.W.	9.08	.73	.307	114	114	54	1064
J.J.	8.06	.90	.620	158	152	34	1028
G.D. #1	10.32	.87	.53	78	76	56	1203
G.D. #2	10.23	.88	.49	80	81	53	1312
M.L.	10.47	.86	.543	65	65	61	1203
T.L.	9.93	.83	.446	23	21	56	976
R.T.	10.19	.87	.48	73	74	52	1210

Five Gm. of sodium chloride were added daily to the diets of S.M., W.W., and J.J., and are included in the above dietary analyses. During the period of dextran administration the dietary salt supplement was withdrawn, and an equivalent amount was given in the infusions. G.D. No. 2, M.L., and T.L. received supplemental intravenous saline daily during the control period immediately preceding dextran administration, corresponding to the quantity given in the dextran infusions. The two remaining subjects, G.D. No. 1 and R.T., received no supplemental salt, and consequently their sodium chloride intake was considerably higher during the dextran period.

Dextran was administered intravenously to all subjects; 6 per cent dextran in 0.9 per cent sodium chloride solution was given in five experiments, in the following dosage:

Sub.	Daily infusion cc.	Gm dextran daily	Days given	Total dextran dose, Gm.
G.D. #1	2000	120	6	720
G.D. #2	2000	120	6	720
M.L.	2000	120	4	480
T.L.	2000	120	2	240
R.T.	1000	60	10	570

Subject R.T. received only 30 Gm. of dextran on the eighth day of administration, thus accounting for a total dose of only 570 Gm.

Twelve per cent dextran in 0.5 per cent sodium chloride was administered to three subjects: S.M., W.W., and J.J. Each received 1000 cc. daily (120 Gm. dextran) for six days, a total dose of 720 Gm.

For brevity's sake, the period of dextran administration will hereafter be referred to simply as the "dextran period."

Suitable control observations were made prior to the dextran period to allow each subject to equilibrate metabolically with the diet. This usually required 10 to 18 days. Balance studies were continued following dextran until metabolic data returned to control levels.

Serum electrolyte and protein concentrations and venous hematocrit were determined at the beginning of each metabolic period, and more frequently when indicated. Urine dextran levels were determined daily until excretion became negligible, and serum concentrations were measured at frequent intervals.

The degree of ketosis was estimated from blood ketone determinations in three subjects, and urinary acetone tests in the remainder.

Renal function was evaluated by inulin and para-aminohippurate (PAH) clearance determinations and determinations of maximum tubular excretory capacity for para-aminohippurate (T_{mPAH}) in two subjects, and urea clearance tests in the remainder.

Methods

The analytic procedures were carried out as follows: nitrogen in the urine, diet, and stool was

determined by macro-Kjeldahl; phosphorus in the diet, urine, and stool by a modification of the method of Fiske and Subbarow[5]; calcium in the diet, urine, and stool by the method of Kochakian and Fox[6]; sodium and potassium by internal standard flame photometry; chloride by the Volhard titration, following digestion by the open Carius method.[7] Serum proteins were determined electrophoretically in a Tiselius apparatus[8] and turbidometrically using cationic detergents.[9] Serum and urine dextran was determined by the anthrone method.[10] Inulin and para-aminohippurate were determined as outlined by Goldring and Chasis.[11] Blood ketone concentrations were estimated by a modification of the Scott-Wilson method.[12] The insoluble ketomercuric compound formed was quantitated turbidometrically in a Lumetron colorimeter against acetone-reagent standards. This method, while not precise, proved an adequate gage as to the degree or ketonemia present. Urinary acetone was estimated by Rothera's nitroprusside method. Venous hematocrit was determined as described by Wintrobe. Serum osmotic pressures were determined by the vapor pressure method of Baldes[13] and Hill.[14]

Plasma volume was estimated from changes in hematocrit, according to the following formula:

$$PV_2 = PV_1 \times \frac{H_1(100-H_2)}{H_2(100-H_1)}$$

where PV_2 = unknown plasma volume; PV_1 = control plasma volume; H_1 = control hematocrit and H_2 = hematocrit at time of PV_2

A control plasma volume of 50 cc. per kilogram of body weight was assumed in all subjects. The validity of this equation is dependent upon the assumption that total blood volume varies inversely with the venous hematocrit. The latter premise may be considered valid if: (1) total red cell mass remains unchanged during the period of study, and (2) changes in venous hematocrit are reflective of hematocrit changes in the entire vascular compartment.

Results

Clinical Effects of Dextran

All subjects tolerated the dextran infusions well. There were no vasomotor or pyrogenic reactions. In all instances weight was gained during the dextran period, from 3 to 5 Kg. in those subjects receiving large amounts, 720 Gm. over a six-day period. Headache, presumably due to expanded plasma volume, was occasionally experienced several hours after an infusion.

In two subjects it was necessary to discontinue the injections because of complications. T.L. developed evidence of pulmonary congestion after two days (240 Gm.) of dextran. This patient had no previous evidence of cardiac disease, but was mildly hypertensive and was in an older age group. It was apparent that the rapid plasma volume expansion routinely resulting from dextran administration precipitated cardiac failure in a subject with a reduced cardiac reserve.

Subject M.L. experienced an exacerbation of her chronic dermatitis, manifest on the third day of dextran administration. The skin lesions became exudative and hemorrhagic. The severity of the exacerbation necessitated discontinuance of dextran administration, and the large protein and electrolyte losses from the skin invalidated subsequent metabolic data.

A bleeding tendency was noted in M.L., and in all subjects receiving 12 per cent dextran. J.J., W.W., and S.M. showed microscopic hematuria and bleeding from venipuncture sites and the gums. In addition W.W. had epistaxis, a subconjunctival hemorrhage, and prolonged bleeding from shaving cuts. M.L. experienced a brief episode of metrorrhagia, in addition to the bleeding into the skin lesions.

In all instances bleeding appeared after two to four days of dextran administration, and subsided two days after discontinuing the infusions. Bleeding time was prolonged in these subjects, and clotting time normal. Prothrombin concentration and consumption in J.J. and W.W. were not significantly depressed. No hematologic studies were performed in the remaining subjects in this study.

Hemocrit and Calculated Plasma Volume

As shown in table 1, in all subjects the venous hematocrit fell during dextran administration. This was most striking in those subjects receiving 12 per cent dextran, in whom an average decrease of 23 per cent below control values was observed. Two subjects (W.W. and J.J.) showed a continuing fall in hematocrit after the discontinuance of dextran, reaching a low point in 16 and 13 days respectively. (See figures 2 and 4.) A similar, but less marked, tendency was noted in T.L.

TABLE 1.—*Hematocrit and Plasma Volume Changes Induced by Dextran*

Subject	Control		After Dextran				Maximum Change					Final Observation		
	Hmct. %	Calc. Plasma Vol. Liters	Hmct. %	% Change	Calc. Plasma Vol. Liters	% Change	Days After Dextran	Hmct. %	% Change	Calc. Plasma Vol. Liters	% Change	Days After Dextran	Hmct. %	Plasma Vol. Liters
S. M.	46	3.82	35	−24	6.04	+58	1	35	−24	6.04	+58	46	42	4.49
W. W.	47	3.30	34	−28	5.68	+72	16	31	−34	6.51	+97	16	31	6.51
J. J.	45	3.28	37	−18	4.56	+39	13	30	−33	6.24	+90	58	43.5	3.48
G. D. #1	47	2.76	39	−17	3.83	+39	1	39	−17	3.83	+39	90	45	2.99
G. D. #2	45	3.28	42	−7	3.71	+13	*	39	−13	4.20	+28	17	43.5	3.48
M. L.	48	3.64	40	−17	5.05	+39	1	40	−17	5.05	+39	42	45	4.10
T. L.	46	4.34	40.5	−12	5.45	+26	13	39.5	−14	5.65	+30	13	39.5	5.65
R. T.	51	3.31	43	−16	4.57	+38	1	43	−16	4.57	+38	15	44	4.38

Note: In this and subsequent tables, the term "After Dextran" denotes observations made on the morning of the day following the last of the series of dextran infusions.

* Maximum hematocrit change in this subject occurred after the first two days of dextran administration.

The maximum hematocrit depression appearing in G.D. no. 2 after only two infusions may be related to prior plasma volume expansion by the administration of intravenous saline in the predextran control period. In all subject the hematocrit remained depressed throughout the period of observation, which exceeded 40 days in four subjects.

Plasma volume expansion, calculated from the venous hematocrit, exceeded 90 per cent of control levels in two subjects (table 1).

Serum Proteins

Serum protein concentration fell in all subjects during the dextran period, the decrease ranging from 22 to 53 per cent below control levels (table 2). In all instances, the globulin concentration fell relatively more than the albumin. Total circulating protein appeared to decrease in all but one subject after the course of dextran, accounted for largely by a fall in the globulin fraction.

In four subjects there was an apparent rise of total circulating protein above control levels occurring from 13 to 23 days after the dextran period (table 3). The rise was greater than 30 per cent in all, and appeared to be significant. Failure to observe this phenomenon in the other subjects in this study may be attributable to the relatively short period of observation following dextran, as there was only one subject in this group in whom serum

TABLE 2.—*Effect of Dextran on Serum Protein Concentration and Total Circulating Protein*

Subject	Control						After Dextran											
	Concentration			Circulating			Concentration			% Change			Circulating			% Change		
	TP	A	G	TP	A	G	TP	A	G	TP	A	G	TP	A	G	TP	A	G
	Gm. %			Gm. %			Gm. %						Gm.					
S. M.	6.71	3.64	3.07	256	139	117	3.93	2.27	1.66	−41	−38	−46	237	137	100	−7.4	−1.4	−15
W. W.	7.38	3.53	3.85	244	116	128	3.65	2.00	1.65	−51	−43	−57	207	114	83	−15	−1.7	−35
J. J.	7.44	4.10	3.34	244	134	110	4.0*	2.7	1.3	−46	−34	−61	182	123	59	−25	−8	−46
G. D. #1	6.33	3.97	2.36	175	110	64	4.23	2.79	1.46	−33	−30	−38	162	107	55	−7	−3	−14
G. D. #2	6.70	4.08	2.62	220	134	86	4.99	3.28	1.71	−26	−20	−35	185	122	63	−16	−9	−27
M. L.	6.15	3.10	3.05	224	113	111	2.88	1.51	1.37	−53	−51	−55	145	76	69	−35	−33	−38
T. L.	6.86	3.60	3.26	298	156	142	4.01	2.23	1.78	−42	−41	−45	218	122	96	−27	−22	−32
R. T.	6.7	3.9	2.8	222	129	93	5.2	3.2	2.0	−22	−18	−29	238	146	92	+7	+13	−1

TP—Total Serum Protein; A—Albumin; G—Globulin.

* Determined by cationic detergent method. All other protein determinations done by electrophoresis.

TABLE 3.—*Subjects Showing Rise in Total Circulating Proteins Above Control Levels in Postdextran Period. Tabulation of Maximum Circulating Protein Level*

Subject	Days After Dextran	Concentration			Circulating			% Change Circulating		
		TP	A	G	TP	A	G	TP	A	G
		Gm. %			Gm.					
S.M.	23	6.48	3.92	2.56	344	208	136	+34	+50	+16
W.W.	13	6.40	3.46	2.94	407	220	187	+63	+90	+46
J.J.	20	5.42	3.19	2.23	322	190	132	+32	+42	+20
M.L.	14	6.14	3.02	3.12	310	153	157	+38	+35	+41

TP—Total Serum Protein; A—Albumin; G—Globulin.

proteins were followed for more than 12 days after the dextran period. All patients receiving 12 per cent dextran manifested a rise in circulating proteins, most marked in the albumin fraction. In M.L., circulating albumin and globulin increased approximately in equivalent amounts. Figures 2 through 4 depict this post dextran rise in circulating proteins in the subjects receiving 12 per cent dextran. As noted there, this rise appears to occur as serum dextran concentration and total circulating dextran levels are falling. This change was accompanied by a concomitant rise in plasma volume in all three subjects, despite the fact that dextran was leaving the circulation. In contrast, figure 1 reveals the changes seen in G.D. no. 2, in whom a significant rise in circulating protein and further expansion of plasma volume were not observed. This was the usual course seen in the remaining patients in this study, although observations were of shorter duration in this group.

Fate of Administered Dextran

Calculations of the fractions of dextran excreted, circulating and unaccounted for were made on each subject and are presented in table 4. Urinary excretion was maximal during the dextran period, when it accounted for over 50 per cent of that injected, in all but one subject. Excretion rapidly diminished thereafter and was negligible several days after the dextran period.

The maximal serum dextran concentrations shown in table 4 were present at the end of the dextran period. Levels of 3170 mg. per 100 cc. were attained in subjects receiving 12 per

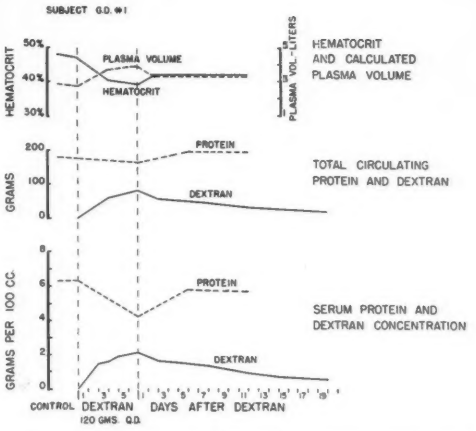

FIG. 1. Serum protein and venous hematocrit changes induced by dextran administration in G.D. no. 1.

cent dextran, significantly higher than in those receiving 6 per cent dextran in equivalent amounts (G.D. no. 1 and G.D. no. 2). It should be noted however, that in the studies on G.D. that fraction of administered dextran circulating was the lowest in the entire group, and may not be representative of the subjects receiving 6 per cent dextran. Serum dextran concentration decreased gradually after the dextran periods, as depicted in figures 1

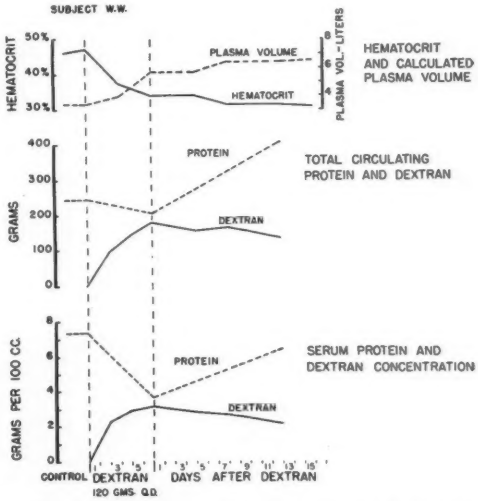

FIG. 2. Serum protein and venous hematocrit changes induced by dextran administration in W.W.

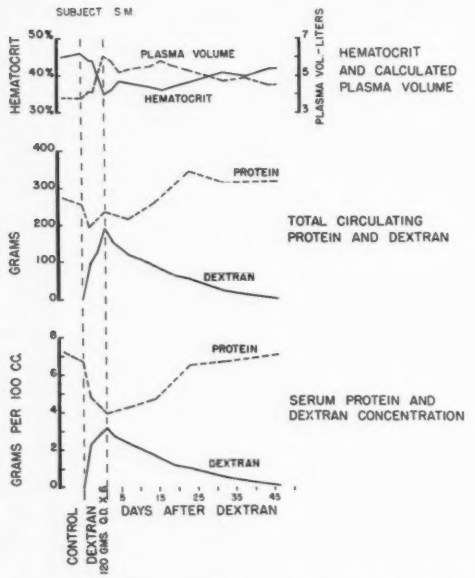

FIG. 3. Serum protein and venous hematocrit changes induced by dextran administration in S.M.

through 4. In J.J. (fig. 4), there was an apparent secondary rise in dextran concentration at 8 and 10 days after the dextran period, accompanied by a transient fall in serum protein concentration. This suggests that

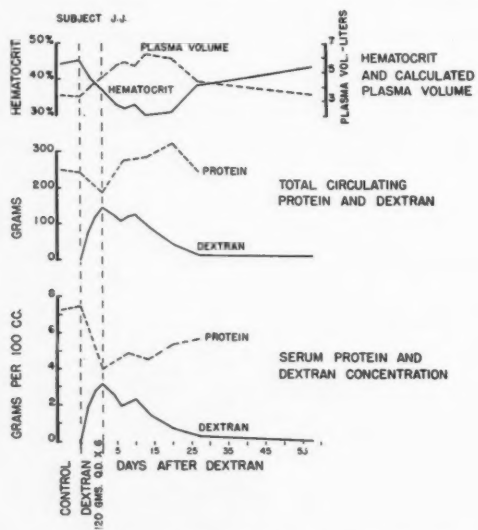

FIG. 4. Serum protein and venous hematocrit changes induced by dextran administration in J.J.

TABLE 4.—*The Fate of Administered Dextran*

Subject	Grams Dextran Given	Days of Therapy	Maximum Serum Conc. mg. %	Circulating Dextran Gm.	Urinary Excretion Grams		Fate of Dextran at End of Dextran Period % of Total Dose		
					Dextran Period	Total	Circulating	Excreted	Not accounted for
S.M.	720	6	3170	191	412	476	26.6	57.2	16.2
W.W.	720	6	3170	180	425	467	25.0	59.0	16.0
J.J.	720	6	3170	145	412	458	20.2	57.2	22.6
G.D. #1	720	6	2120	81	440	475	11.2	61.1	27.7
G.D. #2	720	6	2400	89	386	431	12.4	52.8	34.8
M.L.	480	4	1940	98	248	272	20.4	51.6	28.0
T.L.	240	2	1440	78	102	121	32.5	42.5	25.0
R.T.	570	10	2400	110	*	*	19.3	*	*

* Accurate measurement of urinary dextran excretion in subject R.T. was not possible, since the patient left the ward for a 24-hour period during dextran administration. The urine passed in this period was not available for analysis.

dextran re-entered the circulation at this point. Serum dextran concentration and total circulating dextran diminished very slowly in W.W. (fig. 2), relative to other subjects in this study, and he showed a continuing plasma volume expansion during this period. Significant serum dextran concentrations, greater than 200 mg. per 100 cc., were observed in three subjects (S.M., J.J., G.D. no. 1) 46, 58, and 110 days following the dextran period. No other long-term observations were made.

Circulating dextran was calculated from the serum concentration and estimated plasma volume. As shown in table 4, 11.2 to 32.5 per cent of administered dextran was intravascular at the end of the dextran period. The remainder of the dextran injected was unaccounted for, and is presumed to have been metabolized or present in extravascular fluid or body cells.

Metabolic Effects

Nitrogen and Phosphorus. As shown in table 5, nitrogen and phosphorus sparing were observed in all subjects during the dextran period, and, occasionally, to a lesser extent in the immediate postdextran control period. This effect was manifested on the second or third day of injections, and rapidly diminished following the dextran periods. Only three subjects (S.M., W.W., and J.J.) were on identical regimens, and in these a comparable metabolic effect might be expected. Complications necessitating the cessation of dextran

TABLE 5.—*Nitrogen and Phosphorus Metabolism in Subjects Receiving Dextran*

Subject	Period	Days	Body Wt. Kg.	Nitrogen (Average per day)				Phosphorus (Avg. per day)			
				In	Urine	Stool	Balance	In	Urine	Stool	Balance
				Gm.				Gm.			
S. M.	I	6	78.22	10.55	11.02	.72	−1.19	.88	.78	.29	−.19
	II	6	76.38	10.55	9.80	.72	+.03	.88	.62	.29	−.03
	III	6	79.24	10.55	11.03	.72	−1.20	.88	.75	.29	−.16
	IV	6	79.22	10.55	11.12	.69	−1.26	.88	.69	.36	−.17
W. W.	I	5	66.42	9.08	9.99	.94	−1.85	.73	.47	.45	−.19
	II	6	66.08	9.08	8.78	.94	−.64	.73	.23	.45	+.05
	III	7	69.42	9.08	10.00	.94	−1.86	.73	.47	.45	−.19
	IV	5	66.51	9.08	10.25	.94	−2.11	.73	.58	.45	−.30
J. J.	I	5	67.22	8.06	11.52	.46	−3.92	.90	.86	.28	−.24
	II	6	65.51	8.06	9.36	.43	−1.74	.90	.56	.31	+.03
	III	6	69.03	8.06	9.85	.43	−2.22	.90	.54	.31	+.05
	IV	3	68.01	8.06	10.43	.43	−2.80	.90	.60	.31	−.01
G. D. #1	I	4	55.72	10.32	12.48	.94	−3.10	.87	.78	.39	−.30
	II	6	55.13	10.32	9.43	.94	−.08	.87	.57	.39	−.09
	III	5	60.00	10.32	10.38	.94	−1.00	.87	.70	.39	−.22
	IV	6	55.93	10.32	13.13	.94	−3.75	.87	.85	.39	−.37
G. D. #2	I	8	57.18	10.23	11.14	.75	−1.96	.88	.81	.39	−.32
	II	6	56.28	10.23	10.41	.75	−.93	.88	.69	.39	−.20
	III	9	59.48	10.23	12.09	.75	−2.61	.88	.80	.39	−.31
	IV	7	54.08	10.23	13.97	.75	−4.49	.88	.81	.39	−.32
T. L.	I	8	88.77	9.93	8.04	.77	+1.12	.83	.55	.31	−.03
	II	2	86.87	9.93	6.80	.77	+2.36	.83	.39	.31	+.13
	III	6	88.66	9.93	6.80	.77	+2.36	.83	.41	.31	+.11
	IV	6	87.54	9.93	7.83	.77	+1.33	.83	.47	.31	+.05
M. L.	I	4	73.80	10.47	7.98	.76	+1.73	.86	.85	.18	−.17
	II	4	72.75	10.47	6.00	.88	+3.59	.86	.56	.24	+.06
	III	8	74.03	10.47	5.25	.95	+4.27	.86	.60	.24	+.02
	IV	5	71.63	10.47	5.96	.95	+3.56	.86	.64	.24	+.02

I—Pre-dextran control period; II—Dextran period; III—First postdextran control period; IV—Following control period.

Body weight recorded is that at the onset of each metabolic period.

administration in M.L. and T.L., and failure to allow for equilibration with an increased salt intake in G.D. preclude a comparative quantitation of metabolic effects in these subjects. The metabolic data on R.T. are incomplete and thus are excluded from this presentation.

An effort has been made to correlate the degree of nitrogen and phosphorus sparing with the amount of dextran unaccounted for in the three subjects receiving 12 per cent dextran. For this purpose, it must be assumed that a constant fraction of this dextran moiety is metabolized from one subject to the next. As shown in table 6, there appears to be a relationship between the metabolic effect and the amount of dextran "metabolized." J.J., in whom the most pronounced nitrogen and phosphorus sparing was observed, showed the largest fraction of dextran unaccounted for.

Glucose was administered to subject S.M. in an attempt to correlate its metabolic effect with that of dextran; 12 and 24 Gm. daily for six day periods elicited no metabolic

TABLE 6.—*Relation between Nitrogen and Phosphorus Sparing and Calculated Dextran Metabolized, during the Dextran Period*

Subject	Dextran Metabolized Gm.	N spared Gm.	Ratio mg. N spared/Gm. Dextran Metabolized	P spared Gm.	Ratio mg. P spared/Gm. Dextran Metabolized
S.M.	117	7.32	62.6	.97	8.3
W.W.	115	7.26	62.7	1.44	12.5
J.J.	163	13.08	80.1	1.62	9.9

effect. On 50 Gm. glucose daily, there was sparing of 0.85 Gm. nitrogen and 0.03 Gm. phosphorus daily. This subject was in a malnourished state at the time of this study. Similar studies have been performed on a normal, well-nourished subject previously. In this instance, amounts of glucose up to 20 Gm. daily had no significant metabolic effect. Thirty Gm. of glucose daily resulted in sparing of 0.47 Gm. nitrogen daily, but had a negligible effect on phosphorus balance. Comparing these two studies, the number of milligrams of nitrogen spared per gram of glucose was 17 in S.M., and 16 in the second subject, an apparently close correlation. The metabolic effect of glucose may thus be contrasted with that calculated for dextran, shown in table 6.

Electrolytes

Sodium and chloride were retained during the dextran period, and were lost during the postdextran diuresis. S.M. and J.J. continued in positive salt balance for as long as six days following dextran, and presumably continued to accumulate extracellular fluid during this period. Moderate potassium retention was noted in all subjects during the dextran period, and balance subsequently rapidly returned to control levels. No significant effects on calcium balance were noted.

Antiketogenic Effects

Semiquantitative urinary acetone determinations were done in all subjects. All developed significant acetonuria during the control observations, which became diminished or absent during the dextran period. Total blood ketones were estimated daily in the three subjects receiving 12 per cent dextran. All showed elevated levels prior to dextran, and only in J.J. was there an apparent effect from dextran administration. In this subject blood ketone fell two days after the dextran period and continued to drop towards normal during the ensuing seven days that observations were made. This apparent antiketogenic effect appeared later than the nitrogen-sparing effect, which was maximal during the dextran period, but which did persist during the postdextran control period.

Blood ketones were also determined during the glucose feeding experiments on S.M. No effect was noted from 12 and 24 Gm. daily, but on 50 Gm. daily blood ketone concentration fell to one third of control levels, indicating a definite antiketogenic effect.

TABLE 7.—*Effect of Dextran on Renal Function*

Subject	Control				Following Dextran				
	GFR cc./min.	RPF cc./min.	RBF cc./min.	TmPAH mg./min.	Days after Dext.	GFR cc./min.	RPF cc./min.	RBF cc./min.	TmPAH mg./min.
S.M.	64	396	712	61	13	79	471	750	76
J.J.	99	424	703	101	10	97	500	746	69

All values corrected to surface area of 1.73M².

Renal Function

Blood urea nitrogen levels, determined in all subjects, and urea clearance tests, done in four, showed no significant change after dextran administration. Results of determinations of maximum tubular excretory capacity for para-aminohippurate, and inulin and para-aminohippurate clearances in two subjects are shown in table 7. Although a fall in tubular excretory capacity for para-aminohippurate in J.J. was observed, the postdextran levels were not significantly depressed below the normal. The initial reduction of renal function in S.M. was unexpected and unexplained clinically.

The urine was examined microscopically at frequent intervals in four subjects. In three, those receiving 12 per cent dextran, transient hematuria and red cell cylinduria were noted during and immediately following the dextran period. No albuminuria was noted. The sediment reverted to normal several days after the dextran period. The fourth subject so examined, M.L., showed no abnormalities of the urine sediment.

Serum Osmotic Pressure

Total serum osmotic pressures were determined in five experiments at varying periods following dextran administration. No significant deviation from control values was noted in any of the subjects studied.

Discussion

The distribution of a foreign macromolecular substance in the human body is initially dependent on molecular size and configuration and ultimately dependent upon the mode of destruction or elimination. The commercial dextran used in these studies is not a homogeneous substance; the range of molecular weights is relatively wide. This variation must be considered with respect to its effects on both the fluid shifts and metabolic changes induced by dextran administration, and on the manner in which this substance is handled by the body.

This study is in agreement with others[15] in demonstrating a metabolic effect from dextran. Subjects in this study were placed on a grossly deficient diet in order to maximize this effect, and, if possible, to quantitate it in terms of the amount of dextran metabolized. The nitrogen sparing, with concomitant phosphorus retention, is presented as evidence that catabolism of tissue protein was retarded during the dextran period. Similarly, an apparent antiketogenic effect was manifested by the reduction in acetonuria in all subjects. On the other hand, the blood ketone concentration was not significantly affected in two subjects, S.M. and W.W., but it should be noted that nitrogen sparing was also minimal in these subjects. J.J., who apparently metabolized more dextran, showed a fall in blood ketones which occurred several days after the dextran period, when nitrogen sparing had virtually ceased. This apparent dissociation of the two metabolic actions is unexplained.

The attempt to correlate metabolic effect with dextran "metabolized" is admittedly inaccurate in the absence of accurate plasma volume measurements from which to calculate total circulating dextran. In addition, until more is known of the fate of dextran in the body, it cannot be assumed that all the dextran unaccounted for, or a constant fraction thereof, has been metabolized. Despite these obvious sources of error, a rough correlation between this calculated dextran fraction and the amount of nitrogen and phosphorus sparing has been observed, as shown in table 6. The chemical structure of dextran suggests that it would be ultimately metabolized as glucose. This concept is supported in this study by the observation of phosphorus sparing in excess of nitrogen sparing during the period of dextran administration, suggesting the active deposition of glycogen. For this reason an attempt has been made to correlate the metabolic effects of dextran and glucose. As noted, less than one-third as much nitrogen was spared per gram of glucose than per gram of dextran unaccounted for. Assuming that the dextran fraction unaccounted for was not entirely metabolized, this discrepancy becomes even greater. On the other hand, the studies on S.M. revealed a marked antiketogenic effect, as manifested by a fall in blood ketones, during administration of 50 Gm. of glucose daily, an effect which was not seen during the administration of dextran to this subject. This lack of correlation between the metabolic effects of glucose and dextran precludes an accurate quantitation of the amount of dextran metabolized in our subjects, but is in itself worthy of comment. It is suggested that the rate of metabolism may be a factor, in that dextran is presumably slowly and constantly being utilized, whereas glucose administered with meals to a calorically deficient subject would presumably be rapidly burned for energy purposes. The observed discrepancy in the antiketogenic effect of these two substances further suggests a fundamental difference in the mode of metabolism or utilization. Present knowledge concerning the metabolism of dextran in animal tissues is scanty, and precludes any definitive explanation of the metabolic effects observed in this study.

Of particular interest is the observation that nitrogen sparing ceased immediately, or within a few days, after the dextran period, despite the fact that serum levels indicated the retention of significant amounts of dextran in the body. This suggests that the circulating dextran was either not available for metabolism or was not susceptible to enzymatic action. The latter possibility appears unlikely, since there is no basis on which to postulate a basic alteration of the chemical structure of this moiety. More attractive is the thesis that this dextran fraction, because of physical properties (namely, molecular weight), remains confined to the

vascular space and does not diffuse into those tissues where enzymatic degradation takes place.

As reflected by changes in hematocrit and electrolyte and water balance, there was significant fluid retention and plasma volume expansion during the dextran period. Thereafter the retained salt and water was rapidly excreted and the body weight fell to control levels. This suggests a rapid disappearance of dextran from the interstitial fluid space, since it is assumed that expansion of this compartment was due to diffusion of dextran into it from the intravascular space. In contrast, the depression of the venous hematocrit persisted and in some cases was intensified after discontinuing dextran.

Although a reduction in red cell mass resulting from dextran administration cannot be positively excluded, acute studies have shown no such change[16]; other marrow elements are apparently not affected by dextran,[3, 16] and, chemically, dextran has no resemblance to substances known to depress hematopoiesis. It therefore seems more likely that the reduction in hematocrit reflects a prolonged and, in most instances in this study, a marked expansion of plasma volume. Of interest is the retention of dextran in the serum for a protracted period after administration has ceased. This may be contrasted with the rapid excretion, during the dextran period, of about 50 per cent of that administered. Other studies have established that dextran of low molecular weight, below 50 and 60 thousand, is rapidly excreted in the urine.[17, 18] In this study there is evidence that a considerable fraction of the administered dextran, presumably of low molecular weight, is rapidly excreted in the urine, and that urinary excretion becomes negligible soon after discontinuing the infusions. A second fraction is metabolized, also rapidly, and the metabolic effect, like the urinary excretion, disappears while dextran remains in the serum in large concentrations. A third fraction, that remaining in the circulation, behaves in a different manner. It persists in the serum for a long period of time and exerts a potent osmotic effect. Further excretion or metabolism of this fraction cannot be demonstrated, although very slow metabolism of this moiety cannot be excluded by our present methods. It seems likely that this represents dextran of high molecular weight which tends to remain in the intravascular space. It does disappear slowly from the blood, but its fate is unknown. Dextran has been demonstrated histochemically[19] and serologically[20] in the reticuloendothelial system of experimental animals after it had disappeared from the blood. Some of this fraction may be engulfed by the reticuloendothelial system and eventually metabolized. However, it will require further study to establish definitively the fate of that portion of administered dextran which is not excreted or rapidly metabolized.

It is generally agreed that the concentration of serum proteins falls with plasma volume expansion by dextran. The acute effect of dextran administration on total circulating protein levels remains controversial. Hammarsten and co-workers,[4] found no change in total circulating protein in normal humans followed for 24 hours after receiving 1000 cc. of 6 per cent dextran. Conversely, other studies have revealed a fall in total circulating protein, particularly albumin, in animal[17] and human subjects[21] infused with dextran. In these experiments, this effect was observed within a few hours after the infusion, and was accompanied by a comparable fall in circulating dextran and a reduction of plasma volume to a level only slightly above its control value. In the subsequent 8 to 12 hours, plasma volume again increased, although gradually, and albumin and dextran re-entered the circulation. These workers believe that acute overloading of the vascular space leads to a loss of fluid into the interstitial space, although no explanation is apparent for the subsequent return of this fluid and consequent re-establishment of an expanded blood volume. The discrepancies between these various studies may be related to the dextran blood levels attained, since, in the studies on dogs,[17] the fall in circulating protein was produced only with large doses of dextran (40 ml. per kilogram). In this regard, Thorsen[2] has noted a relatively greater fall in albumin concentration than in globulin concentration, in acute experiments also, suggesting that al-

bumin may leave the circulation. No information is available on the long-term effects of large doses of dextran on the serum proteins. In this study, no attempt was made to document the acute changes induced by a dextran infusion. During the period of dextran administration there was an apparent fall in total circulating protein in most subjects. This fall was most pronounced in the globulins. Fractionation revealed no change in the relative concentrations of the various globulin components. Following the dextran period, two patterns were seen in those subjects showing an initial fall in total circulating proteins. In two subjects, G.D. no. 2 and T.L., total circulating protein subsequently rose gradually to control levels; at the same time, there was a fall in serum dextran concentration and a rise in venous hematocrit. On the other hand, four subjects (S.M., W.W., J.J., M.L.) showed a significant rise in circulating protein above control values in the postdextran period. In two (W.W. and J.J.) this was associated with a further depression in hematocrit below the level observed immediately after the dextran period. Thus, in two patients there was evidence of further plasma volume expansion while serum dextran concentration was falling. In the other two subjects in this group (S.M. and M.L.) this continued fall in hematocrit was not seen, but both showed a prolonged depression of hematocrit near the level determined at the end of dextran administration. The association of the increase in total circulating protein with the prolonged, or continuing, expansion of plasma volume seems more than coincidental. It is possible to speculate that accommodation to the expanded plasma volume may occur, tending to maintain it at its artificially raised level. It would appear superficially that as dextran leaves the vascular space, plasma proteins enter and, by their osmotic effect, prevent a consequent fall in plasma volume.

The untoward reactions resulting from dextran administration were delayed in onset. The pulmonary congestion induced in T.L. after only 240 Gm. of dextran in two days is especially notable in the absence of any prior evidence of reduced cardiac reserve. It further attests to the potent osmotic effect of this substance. Thereafter, subjects in the older age group were not included in this study. The exacerbation of the chronic dermatitis in M.L. is best explained by the escape of dextran through previously damaged capillaries, serving to increase local edema in the diseased areas of the skin. In this connection, others have found significant concentrations of dextran in burn blisters from patients receiving dextran therapy.[22] A clinical bleeding tendency was noted in four patients, including all three given 12 per cent dextran. Similar observations have recently been reported by Carbone and associates.[16] These workers noted a prolongation of bleeding time in all subjects to whom sufficient dextran was given. Although prothrombin concentration was moderately reduced, this reduction was insufficient to explain the prolonged bleeding time, and was probably commensurate with the expected reduction in concentration of all serum proteins. Clotting time and platelet counts remained within normal range. That bleeding occurred in all subjects receiving 12 per cent dextran might be expected, in view of the significantly higher blood levels of dextran attained in this group. Further study is necessary to define the mechanism involved and to determine whether this is a specific effect of dextran, or one which can be produced with all foreign macromolecular substances.

Previous work in humans on the effect of dextran on renal function is somewhat contradictory. Fleming and co-workers[23] found no impairment of para-aminohippurate or creatinine clearance, or maximum tubular excretory capacity for para-aminohippurate in normal subjects given 500 to 1500 cc. of 6 per cent dextran. Michie and Ragni[24] gave 1000 cc. of 6 per cent dextran daily for six days to five normal subjects and four with pre-existing renal disease, and redetermined renal function four days after the last infusion. They found a reduction of maximum tubular excretory capacity for para-aminohippurate in two normals and three of those subjects with renal disease. Since dextran has been demonstrated in the renal tubule cells of rabbits up to 48 hours after acute administration,[19] at least temporary

impairment of proximal tubular function might be expected. In this study, the decrease in tubular excretory capacity for para-aminohippurate in subject J.J. cannot be considered evidence of functional impairment, since the postdextran level does not deviate significantly from the normal. Subjects receiving large amounts of dextran demonstrated no impairment of glomerular filtration, or renal blood flow which is in agreement with previous studies. Studies on the effect of dextran on maximum tubular excretory capacity in a large group of subjects will be necessary to clarify this still unresolved question. Although the presence of transient microscopic hematuria in three patients might be interpreted as evidence of glomerular damage, albuminuria was not present, and these same subjects showed a generalized bleeding tendency which readily accounts for this finding.

While it might be argued that the amount of dextran administered to subjects in this study is far in excess of the usual clinical dosage, it was deemed necessary to induce changes of sufficient magnitude to render them measurable by our methods. A number of problems which remain unsolved have been raised by this study. While metabolism of dextran has been demonstrated, the site and mechanisms involved remain to be demonstrated. Similarly, a relationship between molecular size and rate of metabolism is suggested, and requires more detailed investigation. Shifts of serum protein out of and into the vascular space are phenomena which at present defy our understanding. The apparent maintenance of a supernormal plasma volume by protein shifts is to us a previously unknown occurrence and raises interesting questions concerning the role of plasma proteins in the regulation of blood volume.

Summary and Conclusions

The administration of large amounts of dextran to human subjects on a metabolic ward has led to further observations concerning the effect of dextran in man.

1. As has been previously established, dextran is a potent osmotic substance which produces marked salt and water retention and rapid plasma volume expansion in normal man. In addition it has been demonstrated that a prolonged depression of venous hematocrit, presumably indicative of increased plasma volume, is induced when large amounts of dextran are given.

2. Rapid urinary excretion occurs during the period of dextran administration, and thereafter quickly diminishes. This is dependent upon molecular weight and in the case of the material studied amounted to over 50 per cent of the total dose in all but one subject.

3. Nitrogen and phosphorus sparing and an antiketogenic effect are produced by dextran administration. These effects are transient, and subside soon after discontinuance of injections. The metabolic effects of glucose and dextran were not comparable in the subjects studied.

4. A fraction of the administered dextran, presumably of high molecular weight, remains circulating over a protracted period of time and produces no discernible metabolic effect. Its ultimate fate in the body is unknown.

5. Serum protein appears to leave the circulation during the period of rapid plasma volume expansion. In some subjects, total circulating protein later reaches supernormal levels. In these subjects there is evidence that plasma volume remains expanded or continues to expand at a time when serum dextran concentration is falling.

6. The administration of sufficient amounts of dextran will produce a prolongation of bleeding time, which may be manifested by a clinical bleeding tendency.

7. No evidence of renal functional impairment secondary to dextran administration was found in this study.

Summario in Interlingua

Grande quantitates de dextrano esseva administrate per via intravenose a humanos con le objectivo de establir un definition plus exacte del effectos metabolic e hemodynamic de iste agente. Omne le studios esseva executate in un section de casos metabolic. Il esseva constatate

que dextrano es un substantia de alte potentia osmotic; in homines normal illo produce un marcate retention de sal e aqua e un prolongate expansion del volumine plasmatic. Rapide excretion urinari occurre durante le periodo de administration; postea iste excretion se diminue rapidemente. Le quantitates assi excernite depende del peso molecular. Un influentia metabolic de dextrano esseva manifeste in le preservation de nitrogeno e phosphoro e etiam in un effecto anticetogene. Isto esseva de natura transitori e dispareva tosto post le discontinuation del injectiones. Un fraction del dextrano administrate—apparentemente de alte peso molecular—persiste in le circulation durante un prolongate periodo e produce nulle observabile effecto metabolic. Su destino final remane incognoscite. Proteina del sero pare quitar le circulation durante le periodo del rapide expansion del volumine plasmatic. In alicun subjectos le total del proteina circulante attinge plus tarde valores supernormal. Il pare que in tal subjectos un constante o accrescente expansion del volumine plasmatic es accompaniate de un reducite concentration de dextrano in le sero. Le administration de sufficiente doses de dextrano produce un prolongation del tempore de sanguination lo que pote manifestar se in un tendentia clinic a hemorrhagia. In iste studio nulle constatation esseva facite que poterea indicar un dysfunctionamento del renes in consequentia del administration de dextrano.

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Does Mitral Stenosis Recur after Commissurotomy?

By Robert P. Glover, M.D., Julio C. Davila, M.D., Thomas J. E. O'Neill, M.D. and O. Henry Janton, M.D.

The ultimate fate of the incised commissure following surgery for mitral stenosis will remain unknown for years to come. A clinical appraisal of patients living five years after commissurotomy and a review of available autopsy material from patients surviving surgery for periods up to four years indicates that valvular restenosis does not occur within the first half decade provided the commissurotomy has been properly performed.

SINCE the inception of definitive cardiovalvular surgery in 1948 there has been much conjecture about the ultimate fate of the incised valve. One of the first questions asked by the patient contemplating valvular surgery is, "Will the valve close again?" To this query the physician has had no authoritative answer than to suggest that recurrence of the stenotic state seems unlikely, provided the full-blown rheumatic state does not return. While such an answer has satisfied the disturbed patient, it is the duty of the physician, if it is possible, to supply more factual information. To that end, the experience, both medical and surgical, in nearly 600 consecutive commissurotomies, performed over a period of five years, has been exhaustively reviewed.

The protean nature of chronic rheumatic valvular heart disease was recognized from the outset as a major obstacle to definitive prognostic conclusions short of several decades of observation. It is to be understood, therefore, that we are not attempting here to predict the future of these surgically treated patients either from the clinical or valvular standpoint. It is a presentation (as the material available lends itself to such analysis), of what has happened to the incised valve during this initial five-year period of observation. Therefore, rather than to draw specific conclusions as to the state of the valve from clinical material alone, the method of investigation which has been adopted comprises a study of the following factors. First and foremost, the operation of mitral commissurotomy must be clearly defined and the technic for its proper performance understood. Second, the pertinent literature has been reviewed to ascertain the experience of others. Third, all available autopsy material obtained in the early and late postoperative period has been studied with particular reference to the incised valve. Fourth, the clinical course and present subjective and objective findings of the oldest commissurotomized patients have been detailed.

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Technical Considerations of Commissurotomy

The rationale and technic of mitral commissurotomy have been published on many previous occasions by the authors and others.[1-11] Only certain features of this operation will be emphasized here as they have a very real bearing on the problem of recurrence of stenosis. The purpose of commissurotomy is twofold as it concerns the valvular lesion of stenosis: to enlarge the mitral orifice and to restore, insofar as the scarred valve tissue will allow, the maximum degree of valve leaflet mobility. To be most effective, this must be accomplished without the production of significant valvular insufficiency. To this end, the anterolateral commissure is cut or split through the

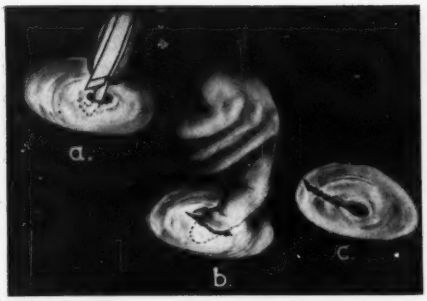

FIG. 1. An adequate commissurotomy necessitates complete anatomic separation of the fused valvular cusps from the stenotic orificial rim out to the annulus (c). This can be achieved best by initiating a cut through the thickened portion of the fused commissure at the rim of the orifice (a) and subsequently by either digital separation of the remainder of the commissure (b) or when necessary by multiple cuts with the hooked guillotine knife.

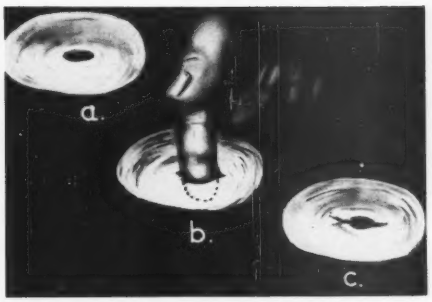

FIG. 3.—An inadequate commissurotomy, a simple thrust of the finger through the stenosed orifice (a), does not constitute acceptable valvular surgery. As the finger is thrust through the valve (b) a sensation of "give" may be felt. This is due to slight tearing at the angles, but if the procedure is limited to this maneuver the result will be an inadequate increase in the size of the orifice and little, of any, improvement in valvular motion (c).

area of pathologic fusion outward to the myocardium at the atrioventricular annulus (fig. 1). Thus, the two mitral leaflets are completely separated from each other at this angle and are capable of motion independent of each other, there now being no scar tissue bridge between them. In addition, the finger must be advanced through the valve opening for subvalvular dissection. Ofttimes, chordae tendineae and papillary muscle, fused to each other or to the myocardial wall, can be gently freed to add considerably to the desired overall improvement in valve function (fig. 2). Such a newly constructed valve orifice should readily admit the introduction of two fingers, placed side by side; this constitutes the ideal valve opening when dealing with the tissues usually encountered in rheumatic mitral stenosis. Under these circumstances, the posteromedial commissure may be left intact, for it is usually short, heavily indurated and ill-defined, due to the fusion and shortening of the chordae tendineae peculiar to this location in the valve ring. Frequently, however, a centimeter or so of commissural separation can be accomplished in this area as well, to further enlarge the orifice and to increase the mobility of the valve leaflets.

FIG. 2.—Subvalvular dissection is of great importance in many instances in order to achieve maximal mobility of the cusps. (a) Illustrates the fused mass of thickened and shortened chordae tendineae which restrains motion of the leaflets even though the commissural fused cusp edges have been separated. (b) Separation of this subvalvular mass can be accomplished by finger dissection in most cases. (c) The desired result will be obtained in this manner.

Anything less than the above-described commissurotomy is not considered to be ideal, although, to be sure, the distortion of the valve tissues, the imbedded calcium, the shortened, fused and puckered chordae and papillary muscles may prevent the operator from accomplishing this desired ideal in a number of cases. It must be the pathologic changes of the valve tissues that dictates the limitations of the operative procedure and not the surgeon's ignorance of what constitutes an ideal commissurotomy. Within the past two years, intracardiac valvular surgery of this type has suddenly become the ambition of almost every

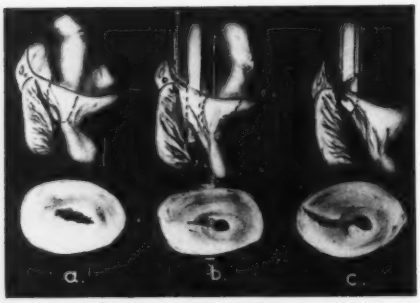

FIG. 4.—In some instances, even though care is taken to attempt a separation of the cusps out to the annulus, the false impression that this is achieved may be the result of "pressing" the relatively pliable edge of the membranous "cone" against the myocardial wall (a and b). This pitfall is indicated as it may occur in the course of finger dissection or even when cutting of the commissure is attempted with a straight bladed instrument. (c) The guillotine knife with the blunt hooked end is particularly valuable in assuring that the membrane be held and effectively cut.

surgeon who has ever had occasion to open the thorax, and, as a result, commissurotomies are now being attempted by many operators who have had little or no experience in this field; nor a complete understanding of the fundamental surgical goal. For example, there are many who merely thrust the index finger through the tiny stenotic valve orifice, feel the tissues split to a degree on either side and rapidly withdraw the finger, feeling that a proper commissurotomy has been performed. Under these circumstances, the valve leaflets have not been adequately separated and a considerable bridge of fused tissue remains to prevent adequate restoration of valve motion (fig. 3). Most certainly such an incompletely divided commissure may act as the locus for reagglutination, either because of the proximity of the raw cusp margins, or from the deposition of fibrin and particulate matter leading to thrombosis. Even more experienced operators seem unaware of the fact that the base of the valve cone at the lateral angle of the commissure may lie parallel to the ventricular myocardium and be unrecognized without specific exploration for it. Such pliable commissures might well be opened by finger pressure or with a straight bladed knife or both to the point where the commissural tissue lies against the myocardium, leaving a centimeter or more of commissure unopened, with the operator under the impression that the valve angle had been completely opened (fig. 4). For these reasons and others, the dull hooked knife with a guillotine blade is preferred and used whenever the commissural tissues do not separate readily with a moderate degree of finger pressure. An understanding of these fundamental principles in the technique of mitral commissurotomy is obviously essential for the intelligent evaluation of the valvular status of patients so treated.

REVIEW OF LITERATURE

A review of the literature reveals very little data on the subject of stenosis recurring after surgical intervention. This is understandable since the follow-up period of observation in the experience of most surgeons has been short. Five specific instances in which a recurrence of stenosis is postulated have come to the attention of the authors. In the cases reported by Jordan and Hellems[12] and by Donzelot and others,[13] the suspicion that an adequate commissurotomy was not performed is entertained. In the latter instance it is stated in the protocol that due to the precarious condition of the patient the procedure was limited to a single thrust of the finger through the stenotic orifice. The statement, attributed to Wood,[14] that in 5 per cent of the cases followed by his group, there was reactivation of the rheumatic process and recurrence of stenosis needs considerable clarification and more detailed information. One would hardly think that he meant to imply that the two conditions are one and the same. Janton[15] and Soloff,[16] the first to call attention to the occasional recurrence of rheumatic activity following surgery on the rheumatic heart, have not observed what could be considered a return of structural valvular stenosis, and indeed they feel, that such a stipulation could hardly be made on clinical grounds alone. Avery and Priest[17] have noted the reagglutination of an adequately opened posteromedial commissure in a heavily calcified valve. In such a badly damaged valve and with the commissurotomy necessarily localized to

the posteromedial angle (the area of least excursional motion even in a normal valve), sufficient valve motion could obviously not be restored; under such circumstances one might rarely expect a thrombus to plug the orifice in this manner. In a case early in the experience of Julian,[18] an anterolateral commissurotomy was thought to have been made, enlarging a 5 mm. orifice to 18 mm. The excellent clinical result obtained terminated in 18 months with a recurrence of the patient's original symptoms. At reoperation, "the mitral valve orifice was again found to be 5 mm. in length, but this time, being somewhat more expert with the handling of such fibrous valves, the opening resulting from incisions along both anterolateral and posteromedial commissures was over 3 cm. This patient has again recovered normal activity." Obviously the original commissurotomy was either very small or consisted primarily of orificial dilatation.

Muller[19] has reported the findings in postoperative autopsies on two patients, one at seven months, in whom no evidence of restenosis was found. Brock[20] has stated that in the absence of reactivation of the rheumatic process restenosis is unlikely. He elaborated on the mechanism of possible reocclusion in that situation in which a mass of fused chordae and papillary muscles might produce a subvalvular site for thrombosis. In this regard, it might be permissible to theorize and speculate on the possible mechanism of fusion of incised valve elements whether effected by old or recent rheumatic activity. In mitral stenosis, at the stage in which commissurotomy is performed, one is dealing with a densely scarred structure which has admittedly no blood supply within its densely fibrous or calcified substance. Tissues with these characteristics are notorious for their poor healing qualities. On this basis and in the absence of a reactivation of the rheumatic process which involves the valve elements proper, it seems quite unlikely that fusion can recur. However, due to inadequate pliability of the leaflets, or due to distorted anatomy (foreshortening and fusion of the chordae tendineae and papillary muscles into a dense subvalvular column), when such a commissure is cut, a deep welled crevice is created. Vascular particulate matter and local stasis of blood can predispose to thrombosis or deposition of fibrin leading to subsequent organization and fibrosis. Hence narrowing of the mitral orifice may result. As stated, the prevention of this form of recurrence depends to a great extent upon the adequacy of the technic of commissurotomy.

In just under 600 cases of mitral commissurotomy, there has been a total of 42 deaths in the late postoperative period. The ultimate clinical course and the cause of death in five of these cases is not known. The remaining 37 cases were adequately followed to the time of their demise. Of these the longest survival following an adequate commissurotomy was 36 months. There was not a single instance in this group in which death could be attributed to the recurrence of mitral stenosis. As shown (table 1) the cause of death in the majority was the far advanced stage in which the patient presented himself for surgical treatment. That is, these patients were in the group referred to as a functional stage V, in which irreversible cardiac, pulmonary, hepatic and/or renal changes existed. Such cases do not obtain benefit from commissurotomy. In a significant number of patients, mitral insufficiency or aortic valvular disease was an important or even major factor in the ultimate outcome. In several, existing mitral insufficiency was further aggravated by surgery.

TABLE 1.—*Causes and Contributing Factors in the Deaths of 42 Patients in the Late Postoperative Period*

	Cases
1. Stage V cases which showed progressive failure due to irreversible state despite adequate commissurotomy	5*
2. Stage III to V cases in which multivalvular disease was an added factor	16*
3. As in 2 but mitral insufficiency was aggravated by surgery	10*
4. Pure mitral stenosis but in which significant mitral insufficiency was produced surgically	1
5. Adequate commissurotomy was not technically possible	3
6. Subacute bacterial endocarditis	1
7. Unknown	6*
	42

* One case in each group had presumed rheumatic activity postoperatively.

TABLE 2.—*Length of Survival in 31 Autopsied Cases*

Deaths within 24 days of surgery	
In O.R.	6 cases
Within 24 hrs.	5 cases
24 to 72 hrs.	4 cases
3 to 24 days	5 cases
	20
Late Deaths	
4 to 5 wks.	3 cases
8 to 13 wks.	3 cases
7 to 10 months	2 cases
15 to 18 months	3 cases
	11

There was one patient with "pure stenosis" in whom severe mitral regurgitation was produced surgically. Group 5 in table 1 is of importance. These three patients can be said to have died of essentially unrelieved mitral stenosis. In none of these was an adequate commissurotomy technically possible and therefore their obstructive lesion was not relieved. In one case the appendage was so tiny (child, age 4) that a finger could not be introduced into the atrium and despite a blind attempt to open the valve by means of a curved Kelly clamp the diastolic murmur persisted without change in quality. This patient died in congestive failure during another attack of rheumatic fever 22 months later. A second case had a densely calcified, thickened, puckered valve, and, although a slight commissural separation might have been accomplished (initial valve orificial size, one finger; opened to one and one half fingers), the course was one of gradual deterioration until his death 42 months postoperatively. The third patient (early in this series) had a completely thrombosed and obliterated appendage and the commissurotomy was attempted through a pulmonary vein (not a recommended technic). Access to the valve was unsatisfactory and although a slight separation was achieved, it was totally inadequate. The patient died 15 months later. In none of the three patients was there any postoperative clinical improvement. In only this last case was autopsy permitted and examination of the valve revealed the original slight degree of separation but no evidence of restenosis.

VALVULAR FINDINGS IN 31 AUTOPSIES

Thirty-one autopsies upon patients dying after mitral commissurotomy are reviewed. Table 2 lists the survival periods of these cases. In the postmortem protocols of 20 patients who died within the first 24 postoperative days, there was no evidence that restenosis had occurred nor was there any thrombotic material or granulation tissue in or about the incised commissures. In all, the separation of the incised commissures was clearly evident. Figure 5 shows the valve in one of these cases in which a typical commissurotomy is seen.

The findings in 11 autopsies performed upon patients who died in one to 18 months postoperatively are available. One of these patients who survived surgery for 13 weeks was presumed to have suffered a flare-up of rheumatic activity postoperatively. There was no indication of acute valvulitis in this case. In none of the 11 was there any evidence to suggest endothelialization of the cut commissures nor was there evidence of restenosis by any mechanism. Material currently available on five of these cases is presented and pictures of these five valves are reproduced in figure 5. Microscopic sections from the anterolateral commissure in four cases are illustrated in figure 6. It is of interest to note that even in the one case autopsied of the three noted in table 1 (E) who had had an inadequate commissurotomy, the partial separation has persisted (not illustrated).

CLINICAL ANALYSIS

Although even a meticulously accurate clinical appraisal of the operated patient cannot be used as specific evidence to either prove or disprove the state of the incised valve, such an analysis lends considerable weight when it tends to corroborate the observed pathologic findings. Rather than indulge in a detailed discussion of the total number of cases in this entire series, it seemed wise to concentrate upon those patients, treated consecutively, who have lived the longest period of time and who, therefore, represent the best available span of observation. Ten patients in various clinical stages of rheumatic heart disease with mitral

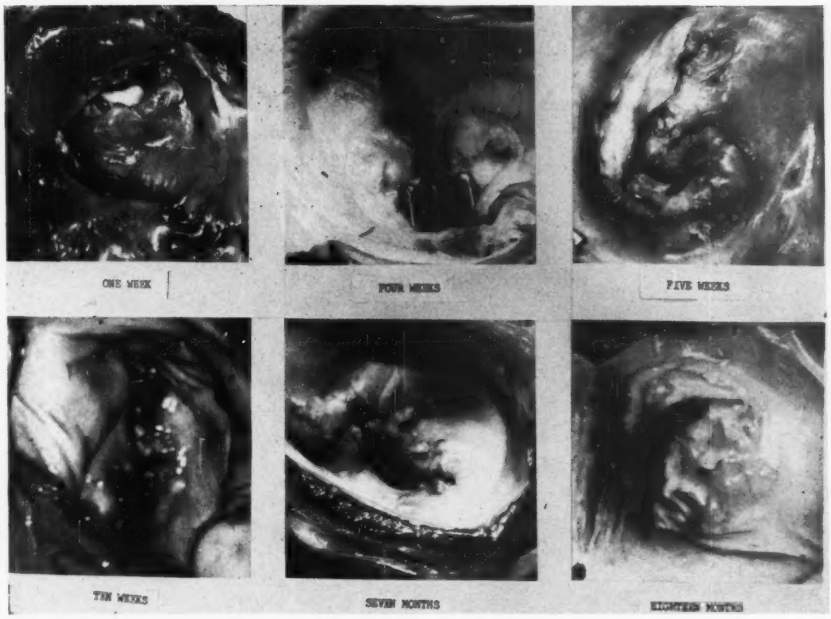

FIG. 5.—Photographs of six valves at various intervals after commissurotomy. The anterolateral commissure, which has been cut in all these specimens, is shown towards the top of the illustrations. Note that in all cases the surgically produced separation has remained. Furthermore, there is no gross evidence of new cicatrization, fibrin deposition, granulation tissue reaction, nor thrombosis. Note that these valves are all badly scarred and calcified. The five-week old specimen is interesting because this case died of a purulent pericarditis and bacterial endocarditis. A zone of septic vegetations is present, located in the region of the annulus and atrial wall. There were no such vegetations on the margins of the valve cusps nor on the cut edges of the commissure. The 18-month specimen is from a patient who had an excellent clinical result and who died in a traffic accident (commissurotomy done elsewhere).

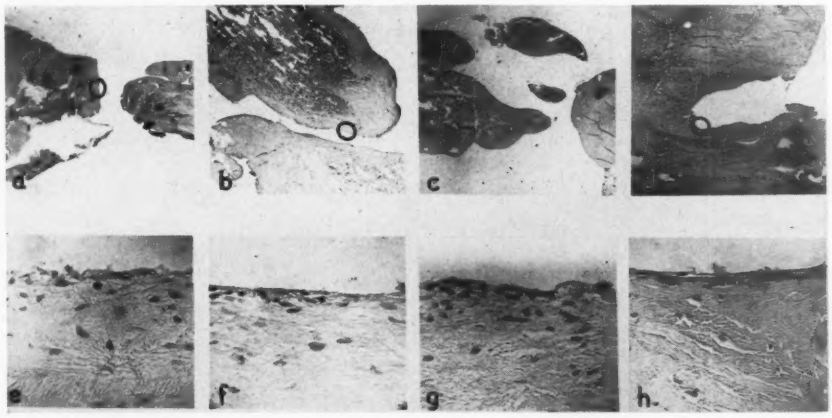

FIG. 6.—Sections from four valves taken at various intervals after commissurotomy: (a) three days, (b) four weeks, (c) five weeks, (d) seven months. The magnification is 10×. The figure shows the cut commissures separated and the surfaces of the cut of the previously fused cusps. (e, f and g) High power microphotographs of the cut edge which is marked by circles in a, b and d respectively. (h) A section from valve (d) from a zone upon which no surgical manipulation was carried out. The magnification of the last four illustrations is 400×. No evidence of healing or reagglutination can be detected in these specimens.

stenosis were subjected to commissurotomy in 1949. Three of these died in the immediate postoperative period. The other seven are living today, four and one-half to five and one-half years later. As such they are among the oldest living postcommissurotomy patients. So that the reader may form his own opinion as to their present status, individual summaries of the case histories have been prepared.

In the opinion of the authors, the referring physicians and the patients themselves, five of these patients (cases 1, 3, 5, 6 and 7) have obtained an excellent functional result. They are asymptomatic, require no cardiac medication and are living a normally active life. One (case 4) is improved but has not as yet reached her ultimate status since a tricuspid commissurotomy was necessary just eight months ago. One (case 2) is unimproved; in fact her condition understandably is slowly deteriorating after having obtained moderate improvement for three years. In view of her postoperative course it would seem likely that her myocardium is failing in the face of a valvular stenosis inadequately opened due to the type of pathology encountered.

For the past two years we have been impressed by the fact that the obvious functional improvement obtained in 75 per cent of our patients is not routinely reflected in the objective cardiac findings. For example, in these seven patients, five have retained some element of their original diastolic murmur although there is some diminution of the pulmonic second sound. Two have mitral systolic murmurs of the same intensity as heard before surgery.

Fluoroscopically and by complete roentgenographic studies, two patients (cases 1 and 3) show reduction in their cardiac size to practically normal limits, three show no appreciable change (cases 2, 5 and 7) and in two there is some increase in cardiac size (case 4 and 6). In general those who have shown a decrease in overall size (most patients will show a diminution or even a concavity in the pulmonary conus-pulmonary artery segment of the left border silhouette probably from obliteration of the left auricular appendage) were the smaller hearts initially. One must be careful to recognize in the larger hearts that postoperative reduction in size may merely mean that the patient was in subclinical failure just prior to or at the time of surgery. In such instances a more rigorous dehydration regime might have further reduced the size of the cardiac silhouette preoperatively comparable with that noted postoperatively, and which fallaciously has been attributed to the surgical intervention. These factors may greatly confuse much of the roentgen data forthcoming in the future.

That there was little or no significant electrocardiographic change observed was somewhat surprising. The four cases in normal sinus rhythm and the three in auricular fibrillation prior to surgery remain the same to date. Minor changes in the voltage and direction of the various complexes, while varying from time to time, have remained essentially unchanged in five (cases 1, 2, 3, 4 and 6). In cases 5 and 7, there was a slight decrease in the magnitude of the right axis deviation accompanied by an increase in the voltage of R waves in leads V_5 and V_6.

Physiologic studies are playing an ever increasing role in evaluation of patients undergoing cardiac surgery. In many instances, too much reliance has been placed on the cardiac catheterization findings originally regarded as almost "factual without question." Most observers now agree that such studies when performed on patients with acquired heart lesions must not be taken "out of context" but are of value only when subject to correlation with all other findings including clinical appraisal, fluoroscopic and electrocardiographic observations.

Each of these seven patients has been subjected to pre- and postoperative catheterization studies although these studies are by no means complete. The original examinations in 1949 were carried out during the embryonic phase in the development of our laboratory and consist of pressure recordings in the pulmonary artery and right heart chambers only. The results are tabulated in table 3. A significant decrease in pressure was obtained in four instances (cases 1, 3, 5 and 6) all of whom have remained clinically excellent to date. In case 7, also considered to be an excellent result four

TABLE 3.—*Catheterization Data*

	Preoperative			Postoperative			
	RA	RV	PA	RA	RV	PA	Months
1. J.B.		90/17 (41)			48/3 (18)		20
2. E.W.	12/3	82/2	84/38	5/?	56/1	63/19	1
3. V.S.		141/5 (50)	143/56 (85)		33/14 (20)	36/15 (22)	15
4. R.M.	5/−2	17/−1	14/4.5	9/−1	19/−2	12/2	2
				20−4/0*	25/−10*	14/6*	43
5. T.S.		43/3 (16)	42/12 (22)		27/5 (12)		33
6. J.K.	21/15	60/4	81/31	15/−9	40/0	43/24	1
7. S.G.	1/0	42/?	55/7	†	†	†	

* Prior to tricuspid commissurotomy.
† Technically unsuccessful.

and one-half years later, the early postoperative catheterization was technically unsuccessful. Additional catheterization data at the present time would, of course, be highly desirable and have been suggested to these individuals. Each patient, however, has declined with regret after having already been subjected to two, and some to three such studies. This attitude is understandable if the physician changes places with the patient. Case 4, the patient, who underwent mitral commissurotomy originally and tricuspid commissurotomy four years later, remains an enigma from the catheterization standpoint. Reference to her case history will clarify this statement.

CASE REPORTS

Case 1. J. B., a 32 year old, white, male, miner and truck driver, was admitted to Hahnemann Hospital on Jan. 18, 1949, complaining of chest pain, cough, hemoptysis and shortness of breath. He gave no definite history of rheumatic fever. He had pneumonia in 1942, recovered and was taken into military service but discharged after five and one half months. Shortly thereafter, he noted the onset of periodic bouts of right chest pain accompanied by severe hemoptysis. These attacks occurred about four times a year and lasted one or two days. Exertional dyspnea and intermittent palpitations have been noted for several years. He was unable to work for some time prior to his admission to our service.

Cardiac examination revealed a blood pressure of 110/60. The lungs were clear. The heart showed a long apical diastolic murmur, an exaggerated first sound at the apex and the second aortic and pulmonic sounds equal. Regular rhythm was present at this time although he was known to have had transient atrial fibrillation in the past.

At operation on Feb. 2, 1949, a tight mitral stenosis which would not admit the finger tip was found. The cusp margins about the orifice were rolled and beaded with calcium but the leaflets retained good pliability. The antero-lateral commissure was split and cut and the valve opened to a size which would now admit two and one half fingers. The posteromedial commissure was not opened. (See fig. 7, J. B.) Left atrial pressures taken at surgery were 45/30 before commissurotomy and 14/2 after commissurotomy.

The patient made an uneventful postoperative recovery, was discharged on Feb. 15, 1949, and returned to his previous occupation two months later. He has been working full time in the coal mines and as a truck driver ever since. He requires no medication or dietary precautions. He leads a completely normal and full life in all respects.

Present cardiac findings show a normal sinus rhythm and persistence of an exaggerated mitral first sound with a short, late presystolic mitral murmur with no systolic component.

The preoperative electrocardiograms showed normal sinus rhythm with right axis deviation and notched and deformed P waves in the limb leads. The postoperative tracings have remained unchanged except for slight decrease in the magnitude of the right axis deviation.

Before operation in the posteroanterior projection, the overall size of the heart was estimated to show 2 plus enlargement. The pulmonary artery and the right ventricular outflow and inflow tracts showed 2 plus enlargement. The left ventricle was of normal size, The pulmonary vascular markings were moderately accentuated. Mitral valvular calcification was not detected. At the present time, five and one-half years after operation, the overall size of the cardiac silhouette was considered to show 1 plus enlargement, as was the right ventricular outflow tract and pulmonary artery. There was a diminution in the convexity of the corresponding segment of the left border, noted in the posteroanterior view. In the left lateral view the left atrium appeared unchanged. There was a decrease in the ac-

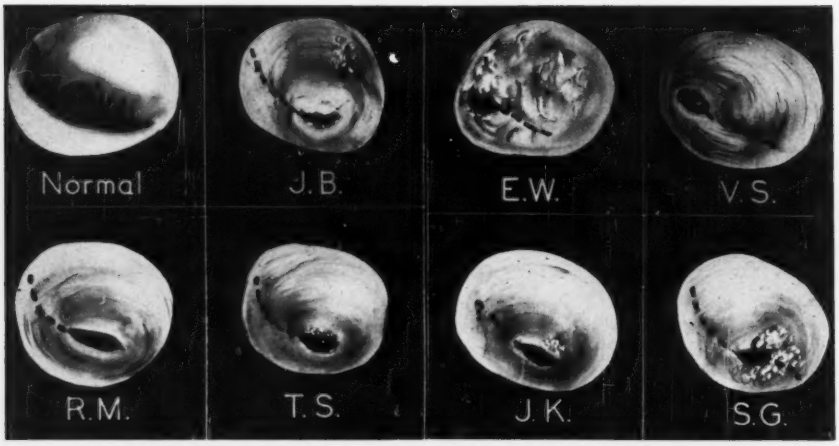

FIG. 7.—Reconstruction of the valvular stenosis and the method by which they were surgically opened in the seven cases presented in the text.

centuation of the pulmonary vascular markings. These changes are comparable with those seen in case 3 (V. S.), whose radiographs are illustrated in fig. 8. Cardiac catheterization data are shown in table 3.

Case 2. E. W., a 38 year old, white, housewife, was admitted to Hahnemann Hospital on April 6, 1949, complaining of "heart disease." She had rheumatic fever at the age of 12. Since that time she had been subject to exertional dyspnea, cough and progressively increasing hemoptysis. She was given digitalis when she was 16 but only for a short time. At the age of 25 she developed congestive failure and had another short course of digitalis therapy. She had been on digitalis from age 28 until admission. Ankle edema had appeared three years ago but none had been noticed in the past two years. In January 1949 the patient had a "renal embolus" and bronchopneumonia. She had progressively increasing dyspnea, orthopnea, cough, hemoptysis and nocturia despite adequate medication and had been unable to do her housework since January 1949.

Her cardiac examination revealed a blood pressure of 132/82. The lungs were clear. The important cardiac findings were: atrial fibrillation with an apical rate of 96, apical diastolic and systolic murmurs, and a moderately accentuated second pulmonic sound. The liver was tender at the right costal margin but not palpably enlarged. No ankle edema was observed.

At operation on April 20, 1949, the mitral valve was found to be greatly distorted by scarring and calcification. Due to the extent and location of the calcified masses, an adequate commissurotomy could not be done. However, the orifice, which originally would not admit even the finger tip, was opened to an estimated one and one half fingers. This was accomplished by splitting and cutting directly through solidly calcified tissues. No restoration of valve motion could be obtained so that the incised cusps tended to remain in close proximity unless the finger was inserted to separate them. (See fig. 7, E. W.) Although a drop in the left atrial pressure was noted (35/16 before and 7/−1 after the procedure), it was stated in the operative protocol that it was doubtful that this procedure would result in lasting improvement.

The patient recovered and was discharged from the hospital on May 10, 1949. Although she was able to do a little housework a few weeks after her operation and is still able to do so, she has not continued to improve. In November 1952 she had an attack of left chest pain which necessitated rest and inactivity. She has been slowly deteriorating ever since this episode, although there has been no increase in her digitalis requirements. She states that she had definitely felt improved postoperatively until November 1952 but has been slowly deteriorating since that time.

Present cardiac examination reveals atrial fibrillation, a loud grade III to IV apical diastolic rumble ending in an accentuated first sound, a rough, loud grade II to III systolic murmur transmitted to the left axilla and a markedly accentuated second pulmonic sound. The liver is 3 fingerbreadths below the right costal margin and is tender. There is 2 plus edema of feet and legs.

The preoperative electrocardiograms showed atrial fibrillation with marked right axis deviation and digitalis effect. The postoperative tracings to date show no significant change.

Cardiac x-ray studies showed a general 3 plus enlargement of the heart shadow in the preoperative posteroanterior view. The pulmonary vascular markings were greatly accentuated. The pulmonary ar-

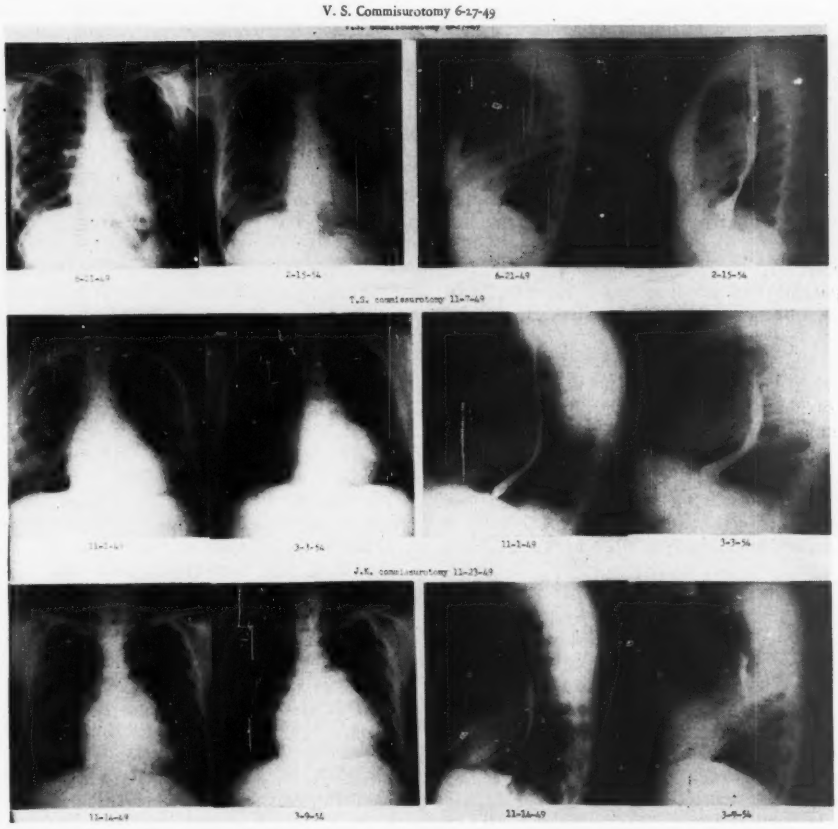

FIG. 8.—X-ray films taken before surgery and several years after to illustrate the three types of changes noted in the seven cases presented. In case V. S. there was an obvious decrease in the size of the cardiac silhouette. In case T. S. there was no significant change in the size of the heart shadow. In these two cases there is significant decrease in the degree of pulmonary vascular congestive markings. There was apparent increase in the size of the cardiac shadow in case J. K. Note the change of the contour in the region of the left auricular appendage in all of these cases. This is due, in part, to the partial amputation of this structure.

tery and right ventricular outflow tract showed 3 plus enlargement. Enlargement of the right ventricular inflow tract was 2 plus; of the left atrium, 3 plus and of the right atrium, 2 plus. The left ventricle was of normal size. Mitral valvular calcification was marked. There was no significant change in the cardiac size postoperatively. Those findings are comparable to those of case 5 (T. S.), whose radiographs are reproduced in fig. 8. Cardiac catheterization data is given in table 3.

Case 2. V. S., a 29 year old, white, female, office worker, was admitted to Hahnemann Hospital on June 20, 1949, complaining of "rheumatic heart disease" since July of 1944, at which time she first noticed dyspnea and cough. One month later she had her first episode of hemoptysis (about 80 to 100 cc. of blood). This was repeated three times in the next three months during which time she developed frank congestive failure. During the ensuing five years she has been hospitalized five times, on each occasion in fulminating failure. She required constant digitalization, diuretics and sedatives. From 1947 to June 1949 she was unable to work except on very sporadic occasions, could not negotiate one flight of stairs and for the most part was confined to her room.

Cardiac examination revealed a blood pressure of 108/64. Her neck veins were engorged. Her lungs were clear. Her cardiac findings revealed a normal sinus rhythm, a sharp and accentuated mitral first sound and pulmonic second sound. There was a long diastolic murmur with presystolic accentuation at the apex followed by a short systolic murmur. The liver was not enlarged and there was no ankle edema.

She was operated on June 27, 1949. The mitral valve was found to be densely fibrosed but not calcified. The tiny orifice was eccentrically placed lying adjacent to the anterolateral myocardial wall. There was no identifiable anterolateral commissure. The posteromedial commissure was split and further opened with two cuts of the knife, the opening being enlarged from an estimated 5 mm. to about two fingers (fig. 7, V. S.). Very considerable valve motion was restored. Left atrial pressures immediately before and after the procedure were 32/17 and 23/7 respectively.

The patient had an uneventful recovery, was discharged from the hospital on July 11, 1949 and returned to her work one week later, against advice. She has worked regularly ever since. In November of 1949 she had a cholecystectomy and in 1952 an excision of a Bartholin cyst. She states that she has had no symptoms whatsoever since her surgery. She has not taken digitalis or any other cardiac medication since leaving the hospital. She now works five eight-hour days a week as a typist. She also does extra work on weekends as a waitress. She leads a full life, dances, bowls and does all her own housework.

Recent cardiac examination revealed a blood pressure of 104/70, a normal sinus rhythm, a grade II apical diastolic rumble with presystolic accentuation, slight accentuation of the mitral first sound and the pulmonic second sound. There is no evidence of congestive failure.

Preoperative electrocardiograms showed normal sinus rhythm with marked right axis deviation. The P waves were broad and notched in the limb leads. At the present time there is normal sinus rhythm, the P waves are now less notched and are decreased in amplitude. The previously marked axis deviation has reverted to normal.

X-ray films preoperatively showed 2 plus cardiac enlargement. The pulmonary artery and right ventricular outflow and inflow tracts were enlarged 2 plus. The left atrium was enlarged 2 plus and the left ventricle was of normal size. The pulmonary vascular markings were accentuated. There was no detectable valvular calcification. At the present time there is a striking decrease in the overall size of the heart (fig. 8, V. S.). Cardiac catheterization data is shown in table 3.

Case 4. R. M., a 36 year old, white female was admitted to Hahnemann Hospital on October 10, 1949, with a history of chorea at age seven. She had another rheumatic flare-up in 1932 and again in 1935. This last episode was followed by severe decompensation for which she was, rather surprisingly, kept in bed for eight years. She had ankle edema, ascites, orthopnea and dyspnea at times despite bed rest. Her condition improved very slowly after prolonged rest, digitalis and diuretics. Just prior to admission she still had edema, dyspnea, cough and orthopnea as well as "palpitations." Occasional hemoptysis had occurred and she suffered a peripheral embolic accident from which she recovered by treatment with conservative measures.

Her cardiac examination revealed a blood pressure of 102/70. The mitral first sound was sharp and the pulmonic second sound accentuated. There was a long, mitral, diastolic rumble and a grade I systolic murmur. Normal sinus rhythm was present. Her lungs were clear. Ankle edema was present. There were full neck veins with marked pulsations.

Mitral commissurotomy was performed on Oct. 14, 1949. The mitral valve was fused into the typical "cone shaped" membrane, pliable but thickened like the kid skin of a glove. There was a minimal regurgitation. The 2 cm. orifice was opened to 4 cm. by cutting the anterolateral commissure. The posteromedial commissure was not cut. (See figure 7, R. M.).

She recovered without incident and was discharged on Oct. 26, 1949. Her dyspnea and edema disappeared for four months. Soon after this she again developed peripheral edema. In 1952, she noted swelling of the face and breasts. Although her breathing had been easier, from that time on she noted progressive exertional dyspnea and fatigability. In May 1953 the diagnosis of tricuspid stenosis was made by cardiac catheterization. On July 17, 1952, she underwent tricuspid commissurotomy. The tricuspid orifice was estimated to measure 13 × 2 mm. It was opened by cutting two commissures to about 10 × 30 mm.

She had a smooth postoperative course and was discharged on July 28, 1953, on a strict medical regimen. Her condition has continued to improve to the present time.

Her present cardiac examination reveals a normal sinus rhythm, a faint diastolic blow to the left of the sternum in the fifth intercostal space and a sharp mitral first sound. She has remained on digitalis therapy.

The preoperative electrocardiogram showed normal sinus rhythm with marked right axis deviation and broad notched P waves in all limb leads. Her present tracing is essentially unchanged.

Preoperative cardiac x-ray films revealed 1 plus cardiac enlargement involving primarily the pulmonary artery, the right ventricular outflow tract and the left atrium. The pulmonary vascular markings were normal. At the present time there is a slight increase in the size of the cardiac silhouette, although, no actual increase in the individual chambers can be detected. The postoperative increase in heart size seen in this case is comparable to that of case 6 (J. K.) illustrated in fig. 8. The cardiac catheterization data is shown in table 3.

Case 5. T. S., a 28 year old, white male, butcher, was admitted to Hahnemann Hospital on Oct. 31, 1949, complaining of shortness of breath. He gave a

history of "growing pains" at age 15. In 1940 he was rejected for military service because of a "murmur." From 1937 until 1940 he had suffered very frequent "colds, one after another." In 1946 he suffered a severe, persistent "cold" accompanied by severe cough and hemoptysis. He was hospitalized and placed on digitalis. He was fairly well after this episode until May 1949 when he went back to work as a meat cutter (having given up this work some time previously). At this time, exertional dyspnea and tachycardia became quite severe and continued to progress until admission.

His cardiac examination revealed a blood pressure of 138/78. The lungs were clear. There was atrial fibrillation, a short apical systolic murmur and a soft, rumbling, mid-diastolic murmur at the apex with presystolic crescendo. The pulmonic second sound was accentuated. His liver was not palpable.

At operation on Nov. 7, 1949, the mitral valve was found to be of the consistency of kid glove skin and the cusp margins were studded with scattered beads of calcium. The orifice would not admit the tip of the finger. The anterolateral commissure was cut and digitally split, accomplishing a final opening of two fingers breadth. The posteromedial commissure was not opened (fig. 7, T. S.). No significant degree of regurgitation was noted. Left atrial pressures immediately before and after the procedure were 37/17 and 19/7 respectively.

He made an uneventful recovery, was discharged from the hospital on Nov. 19, 1949 and returned to work six weeks after surgery. He has been working full time as a butcher ever since. He has required no cardiac medication since surgery and remains completely asymptomatic. He is able to swim and play baseball. He has had no "colds" since surgery. In all respects he leads a completely normal and active life.

Recent cardiac examination revealed a blood pressure of 126/70, atrial fibrillation, murmurs, the same as preoperatively. There is less accentuation of the mitral first sound and the pulmonic second sound. There is also a soft diastolic blowing murmur in the pulmonic area. The preoperative electrocardiogram showed atrial fibrillation with normal electrical axis. His recent tracing reveals no significant change.

X-ray films made preoperatively showed a 3 plus overall enlargement of the heart with moderate increase in the pulmonary vascular markings. The pulmonary artery and right ventricular outflow tract as well as the left atrium showed 3 plus enlargement. The left ventricle was of normal size. At the present time these x-ray findings show no significant change. (See fig. 8, T. S.) Cardiac catheterization data is given in table 3.

Case 6. J. K., a 17 year old, white, male, truck driver, was admitted to Hahnemann Hospital on Nov. 14, 1949, complaining of shortness of breath and frequent "colds." He had had rheumatic fever at ages 6, 9 and 11. He has had progressively increasing dyspnea, orthopnea, cough and hemoptysis. He was unable to work or to participate in sports or recreation with youngsters of his age. He had been on digitalis in recent months.

His cardiac examination revealed a blood pressure of 130/78. His lungs were clear. The cardiac findings revealed atrial fibrillation and a long, mitral diastolic rumble with presystolic accentuation. The mitral first and pulmonic second sounds were accentuated. There was no liver enlargement and no edema of lungs or extremities.

He was operated on Nov. 23, 1949, and the mitral valve was found to be of the consistency of kid glove skin. There was considerable fibrous thickening about the orifice which was too small to admit the tip of the finger. The anterolateral commissure was cut and the valve opened to about one and one-half fingerbreadths (fig. 7, J. K.). Due to the fact that the auricular appendage purse-string suture broke at this point with ensuing hemorrhage no further manipulation or exploration of the valve was accomplished.

The patient recovered without incident and was discharged on Dec. 8, 1949. He did not return to work until a year after surgery when he obtained a job as a truck driver. He worked regularly for two years and was then laid off, remaining unemployed to the present time. He reports that during the past one to two years he has noted some dyspnea on heavy exertion. He remained on digitoxin for more than a year postoperatively but takes no medication now. He is depressed at present due to his inability to find employment.

At last examination in March 1954, by Dr. John Lenox, Myers Clinic, Philippi, West Virginia, he was reported to be much better than before surgery but not quite as well as last year. The lungs were clear. The heart sounds were essentially the same as those noted preoperatively. The pulmonic second sound was less pronounced. Atrial fibrillation was present.

The preoperative electrocardiogram showed atrial fibrillation, marked right axis deviation and digitalis effect. The tracing of March 9, 1954, was essentially unchanged.

The preoperative x-ray films showed a 2 plus overall enlargement of the heart. The pulmonary artery, right ventricular outflow tract and left atrium were enlarged 2 plus. The right atrium and right ventricular inflow tract were enlarged 1 plus. The left ventricle was of normal size. The pulmonary vascular markings were moderately accentuated. At the present time, there is generalized increase in heart size from 2 to 3 plus noted especially in the transverse diameter and the right ventricular outflow tract. The left atrium shows no significant

change. (See fig. 8, J. K.) Cardiac catheterization findings are shown in table 3.

It may be that due to the technical difficulties with the appendage at the time of surgery resulting in considerable hemorrhage a complete commissurotomy (cut out to myocardium) was not accomplished. Possibly he may be re-considered for reoperation in the future should his course ultimately prove to be not entirely satisfactory.

Case 7. S. G., a 35 year old farmer and truck driver, was admitted to Hahnemann Hospital on Nov. 16, 1949. He had no history of rheumatic fever. He complained of progressive dyspnea since 1946 and orthopnea since 1948. He had been digitalized since 1947. There was obvious progression in his dyspnea and fatigue during the past year.

His cardiac examination revealed a blood pressure of 132/90, a normal sinus rhythm and a sharp mitral first sound. There was a long mitral diastolic rumble with presystolic accentuation followed by a grade II apical systolic murmur. The lungs were clear. The liver was not enlarged and there was no peripheral edema.

On Nov. 28, 1949, he underwent mitral commissurotomy. The valve was found to be tightly stenosed, moderately flexible and moderately calcified. It was opened by splitting and cutting both commissures to two fingerbreadths with restoration of some valve function (fig. 7, S. G.).

Following his discharge from the hospital on Dec. 23, 1949, he returned to work as a truck driver. He has been drinking and working excessively and has failed to follow his doctor's advice to moderate his activities. He had some dyspnea on heavy exertion in the early postoperative months but is now completely asymptomatic and able to carry on a normal active life without cardiac medications.

His present examination reveals a normal sinus rhythm, a slightly exaggerated mitral first sound but no diastolic murmur. There is a soft grade I systolic murmur at the apex.

The preoperative electrocardiogram showed normal sinus rhythm with slight right axis deviation and broad notched P waves. His recent tracing shows no significant change other than a decrease in the degree of right axis deviation.

The preoperative x-ray showed a general cardiac enlargement of 2 plus. The pulmonary artery, right ventricular outflow tract and left atrium were enlarged 2 plus. The left ventricle was of normal size. The pulmonary vascular markings were markedly accentuated. At the present time, there is no significant change in cardiac size. There is some decrease in the pulmonary vascular markings. The findings in this case are comparable to those of case 5 (T. S.) illustrated in figure 8. The cardiac catheterization data is given in table 3.

Summary and Conclusions

1. There is as yet no authoritative answer to the question of whether restenosis of the mitral valve will eventually follow commissurotomy. Undoubtedly it will take many years of careful observation before the proper answer can be unequivocally given.

2. The importance of clearly defining the correct technic of mitral commissurotomy, bearing in mind the objectives of this procedure, is emphasized. Only by having a clear understanding of precisely what was accomplished at surgery will it be possible to assess the course of the operated patient and to determine whether restenosis has occurred or whether the original stenotic state was adequately relieved initially.

3. A review of the literature revealed isolated instances of so-called restenosis after mitral valve operations. The authors feel that the conclusion that restenosis had occurred is highly speculative in view of the strong indications that adequate commissurotomy (either due to technical reasons or to the pathology present) was not achieved.

4. In an attempt to obtain at least initial clarification of the problem now that over five years of experience with the operation is available, our entire series of approximately 600 cases (both living and dead) was reviewed.

5. A total of 42 patients have died in the late postoperative period. The causes for these deaths have been outlined. In no instance could death be attributed to the recurrence of mitral stenosis.

6. The autopsy records and material available in 31 cases (early and late deaths) were reviewed, the longest survival among these 31 cases after a technically adequate commissurotomy being 36 months. Again, in no instance was there evidence that death was due to recurrence of mitral stenosis. Serial sections of the valves showed little or no evidence of true endothelialization of the cut surfaces, no evidence of active rheumatic valvulitis and no evidence that any process which might lead to mechanical occlusion of the mitral orifice had occurred. Indeed, many months after operation the tissues and edges of the cut valves appeared

be practically the same as those observed only one or two days after commissurotomy.

7. Seven patients followed from four and one-half to five and one-half years, the oldest living commissurotomized patients, show no clinical, objective or laboratory evidence to justify the presumption that restenosis of the mitral valve has occurred. Five of these patients obtained and have maintained an excellent functional result to date and are living an active, normal life without cardiac medication. The sixth patient is improved but her ultimate functional status cannot now be completely assessed due to the additional performance of tricuspid commissurotomy just eight months prior to this report. The seventh patient, although alive and able to assume minor household duties, is essentially no better now than she was prior to surgery. In this instance the nature of her valvular pathology was such (extensive calcification) that a proper commissurotomy could not be performed at the time of surgery.

The fact that the obvious functional improvement obtained in approximately 75 per cent of our entire series of commissurotomized patients is not routinely reflected in the postoperative objective cardiac findings has been pointed out. This is readily understandable when one appreciates the fact that this surgery is performed for the relief of a *mechanically strictured mitral valve* and not for rheumatic heart disease as a disease complex. Those rheumatic stigmata and changes present in the myocardial and valvular tissues prior to surgery obviously remain after surgery. Should the patient's subclinical rheumatic state continue in the future, and there is no reason to suppose that it may not, unless present day medical therapy (antibiotics and other drugs) is bringing the disease under better control, it is entirely within reason that objective cardiac findings (electrocardiographic changes, heart size and other evidence) will remain essentially unchanged or even, upon occasion, progress. The point is that the patient whose valve has been properly opened with resultant relief of left atrial, pulmonary vascular and right heart hypertension is now in a far better mechanical state to cope with his rheumatic state; therefore emphasis to date has been placed on the patients' improved *functional* status. It is for this reason that the authors have continually stressed *early operative intervention*, once the rheumatic victim has demonstrated the pattern of obstructive symptomatic progression, before cardiopulmonary changes have advanced to a stage where they are on the verge of becoming irreversible.

Thus, based upon the data as presented, it may be stated that the mitral valve leaflets stenosed by rheumatic infection when adequately divided by commissurotomy have shown no sign of either partial or complete return to their previous state within a five year period.

Summario in Interlingua

Le destino final del commissuras incisionate in operationes pro stenosis mitral va continuar incognoscite in le proxime futuro. Un evalutation clinic de patientes ancora in vita cinque annos post commissurotomia e un revista del disponibile datos autoptic ab patientes qui superviveva le operation pro periodos usque a quatro annos indica que restenosis valvular non occurre durante le prime medie decade providite que le commissurotomia esseva executate correctemente.

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Cardiac Resuscitation Following Experimental Arrest by Procaine and Ether

By Martin L. Ryan, A.M., Richard A. Salvador, A.M., and Chester W. White, Jr., M.D.

A method of producing experimental cardiac arrest is described, and the characteristics of arrest are reported. The efficacy of epinephrine, norepinephrine, phenylephrine and acetyl strophanthidin is compared in the resuscitation of hearts stopped by this method.

MANY instances of cardiac arrest during surgery have been reported.[1-3] In this emergency cardiac function may frequently be restored by appropriate early intervention. Methods of resuscitation of the arrested or fibrillating human heart have been the subject of numerous reports and of several reviews.[1, 4-6] Although it has been generally recognized that manual compression of the heart and artificial respiration are important in maintaining oxygenation and circulation of the blood during arrest in addition to promoting the return of cardiac function,[1, 6] conclusions as to the clinical use of drugs to stimulate the heart have been variable.[5-9] Experimental cardiac arrest has been produced by a variety of methods.[10-13] In many of these studies, however, as in the reported clinical cases, the cardiac arrest has not been conclusively established. Resuscitative efforts have frequently been successful, but the value of restorative drugs has remained uncertain either because of inexact diagnosis of arrest or because of the lack of proper controls.

Eggleston and Hatcher[14] reported in 1919 on the actions of intravenous procaine in unanesthetized cats, in which phenol was used as a local anesthetic for surgery. They noted the uniform occurrence of respiratory arrest and a profound blood pressure fall. These events sometimes took place simultaneously, but more frequently the respiratory arrest preceded failure of the circulation. They established cardiac arrest in some of their animals by direct visualization, and stated that an effective heart beat returned spontaneously in some cases. In resuscitation attempts they found artificial respiration and cardiac massage (applied through the chest wall) of little value, unless epinephrine or ouabain was also used to stimulate the heart. It should be noted that their local anesthetic, phenol, may produce depression of the circulation and respiration by itself.[15]

These findings differ from those of Isenberger[16] who used amobarbital sodium before procaine in his animals. He reported that respiratory arrest consistently preceded an asphyxial depression of the circulation which could be reversed by artificial respiration alone. Hulpieu and Cole[17] also reported that intravenous procaine produced respiratory failure before cardiac failure and that artificial respiration with oxygen or air greatly increased the amount of procaine required to produce the circulatory depression. They stated that the "heart stopped" in their experiments, but no criteria for the arrest were given. Schumacker[18] found similarly that respiratory arrest always developed before circulatory stasis when procaine was given intravenously during ether anesthesia; he noted, when the chests of his animals were opened, however, that their hearts were beating weakly after apparent cardiovascular collapse. He found in addition that ether increased the toxicity of procaine in guinea pigs and stated that death was due to medullary paralysis. Other workers have reported that ether increases the toxicity of procaine[19] and cocaine.[20]

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Intravenous procain, then, has severe respiratory and cardiovascular depressant effects, and its toxicity is apparently increased by ether anesthesia. It seemed reasonable that these agents might be used together to achieve a reproducible cardiac arrest, and it was hoped that the circumstances would be benign enough to allow resuscitation.

The purposes of this study were (1) to effect and characterize a reproducible cardiac arrest, and (2) to evaluate several cardiovascular stimulants in resuscitation of the arrested hearts.

Methods

Anesthesia was induced in unselected adult mongrel dogs using ether by a semiopen mask technic. It was maintained by a cuffed endotracheal tube attached to a Wolff bottle. Mean arterial pressure was recorded by a mercury manometer attached to a femoral artery. Standard lead II electrocardiograms were taken. When upper plane 3 surgical anesthesia with constant blood pressure had been maintained for a period of 5 to 10 minutes, attempts to produce arrest were begun.

Procaine hydrochloride was injected intravenously in successively increasing doses of 2, 4, 8, 16 and 32 mg. per kilogram in 0.4 ml. per kilogram. If the initial dose (2 or 4 mg. per kilogram) failed to produce cardiac arrest, a 10- to 15-minute period was allowed for blood pressure and respiration to return to normal before giving the next larger dose. In subsequent injections at 10- to 15-minute intervals, the amount of procaine was doubled each time until cardiac arrest ensued.

The sequence of events following the arrest-producing dose began with respiratory arrest occurring 30 seconds to four minutes later. In the succeeding one-half to three minutes the blood pressure fell to less than 15 mm. Hg, and oscillations in the femoral cannula and mercury manometer disappeared. When this state had been maintained for two to three minutes, the heart was considered in "apparent arrest." Electrocardiograms were taken before and after each procaine injection, at the nadir of blood pressure and at intervals after "apparent arrest." In the first 48 experiments no arrests followed the 2 mg. dose of procaine hydrochloride, and it was omitted in the subsequent work.

Immediately following "apparent arrest," the chest was opened in the fourth left intercostal space and the heart was observed directly. If it was quiescent, or if its movements were so feeble that no aortic pulse was palpable for a period of 30 seconds, arrest was considered complete. In spite of the absence of peripheral circulation, electrocardiographic complexes were still present in some instances. Direct visualization of the heart was, therefore, essential to establish the presence or absence of contractions. After arrest was evaluated by direct observation, resuscitative measures were instituted.

In six animals artificial respiration with oxygen for 20 minutes was the only treatment; in eight others an injection of epinephrine (USP) into the left ventricle was also given. In the remaining 91 animals artificial respiration, with oxygen, manual compression of the heart, and the injection of a cardiac stimulating drug or of 0.9 per cent sodium chloride solution, were used. The respirator was a closed circuit, push-pull type with carbon dioxide absorber and adjustment of inspiratory and expiratory pressure by water manometers; it was operated at 17 cycles per minute. In preparation for cardiac massage all obstructing mediastinal connections of the heart were severed, but the pericardium was left intact. The ventricles were then grasped with the fingers on the dorsal surface and the thumb on the ventral surface, and compressed rhythmically at a rate of 25 to 30 per minute.

The stimulants used were epinephrine hydrochloride (USP), 0.05 mg. per kilogram; *l*-norepinephrine bitartrate, 0.02 mg. per kilogram; phenylephrine hydrochloride, 0.2 mg. per kilogram, and acetylstrophanthidin, 0.1 mg. per kilogram. Sodium chloride (2 ml. of 0.9 per cent) was the control solution. Intravenous, left atrial and left ventricular injections were tried with each agent, five to eight animals being used for each route and agent combination. The drugs were usually administered at the beginning of massage, except in a few experiments where they were given approximately one minute later. When cardiovascular function was restored, as indicated by maintenance of an adequate blood pressure, the chest was closed. Animals which failed to recover consciousness or which showed obvious deficiencies of behavior on the day following the experiment were called "resuscitations"; those which were apparently normal the next day were called "survivals." The term "revivals" will be used to include both "survivals" and "resuscitations."

Three, six and nine minutes following some of the procaine injections in 20 animals, blood samples were drawn. Analyses of the plasmas for procaine were carried out by the method of Brodie, Lief and Poet[21].

In addition to the animals studied under ether, 10 were given procaine hydrochloride in parallel experiments during pentobarbital anesthesia. Total doses of procaine hydrochloride of 240 and 252 mg. per kilogram produced arrest in two dogs, one of which was a survivor; in the second, ventricular fibrillation occurred when cardiac massage was begun. In the remaining eight, doses of 96 to 224 mg. per kilogram produced ventricular fibrillation. It was apparent that pentobarbital anesthesia was unsatisfactory for this work.

Results

Cardiac standstill was produced by rapid intravenous injection of procaine hydrochloride during ether anesthesia in 106 dogs (table 1). The arrests fall readily into three categories according to the residual activity of the myocardium. In 53 animals no myocardial movements or electrocardiographic activity were detected. Twenty-four animals showed persistent electrocardiographic complexes in the absence of myocardial contractions indicating that the electrocardiogram was not by itself a satisfactory index of cardiac status. In 29 animals both electrocardiographic complexes and myocardial twitchings, which were not fibrillatory in character, were seen following the two or three minutes of circulatory collapse. When such action persisted, however, the circulation was ineffective since no pulses were detectable. The probability of successful resuscitation was not influenced favorably by this type of action.

The heart of one animal stopped following the 4 mg. per kilogram dose of procaine hydrochloride, 27 stopped following the 8 mg. dose, 58 following the 16 mg. dose, and 20 following the 32 mg. dose. In no case was a dose larger than 32 mg. required (table 1). Ventricular fibrillation occurred after the injection of 32 mg. of procaine hydrochloride per kilogram in 3 of 23 animals. The cumulated 50 per cent arresting dose of procaine hydrochloride was 19.0 mg. per kilogram (confidence limits 17.0 to 21.3) as estimated by the method of Litchfield and Wilcoxon.[22]

Table 1.—*Cardiac Arrest Produced by Intravenous Injection of Procaine Hydrochloride during Ether Anesthesia*

Dose procaine HCl following which arrest occurred mg./Kg.	No. Dogs	Quality of Cardiac Arrest			Ventricular fibrillation (no. dogs)
		Complete arrest (no. dogs)	Persisting ECG (no. dogs)	ECG and twitches (no. dogs)	
4	1	0	1	0	0
8	27	20	2	5	0
16	58	28	16	14	0
32	23	5	5	10	3
Totals	109	53	24	29	3
		106			

Table 2.—*The Depressor Effect of Doses of Procaine Hydrochloride Not Producing Cardiac Arrest*

Dose procaine HCl mg./Kg.	No. dogs	Control blood pressure mm. Hg mean and S.D.	Nadir blood pressure mm. Hg mean and S.D.	Percent fall in blood pressure mean and S.D.	p of difference control cf. nadir	p of % fall cf. preceding dose
2	48	128 ± 19	114 ± 21	10.6 ± 9.0	<0.01	—
4	97	132 ± 21	107 ± 24	18.9 ± 11.2	<0.01	<0.01
8	79	130 ± 21	92 ± 20	28.4 ± 9.7	<0.01	<0.01
16	17	134 ± 22	90 ± 22	32.6 ± 9.1	<0.01	>0.1

Doses of procaine which were insufficient to produce cardiac arrest uniformly caused a significant fall in blood pressure (table 2), as has been reported by others.[23] Recovery from this effect was apparently complete within the 10- to 15-minute interval between injections. The depressor response following each injection was significantly greater than that after the preceding one (table 2), except for the 16 mg. per kilogram dose. The maximal effect, then, was produced by a total dose of 12 to 14 mg. per kilogram, suggesting that doses in excess of this range are likely to arrest the heart (50 per cent arresting dose = 19.0 mg. per kilogram).

The analyses for procaine showed cumulation of this substance; it did not disappear from the plasma within nine minutes after the 4 and 8 mg. per kilogram doses (table 3). Since the effects of this residual procaine cannot be interpreted, results have been reported as "following" a given dose of procaine hydrochloride or on the basis of total dose.

Seventy-one of 91 animals in which manual compression of the heart was employed were "survivors" and an additional five were "resuscitations." The various states of myocardial and electrocardiographic change which were present at the time of arrest did not appear to influence the effectiveness of the various resuscitative procedures (table 4). One animal was discarded because of mechanical failure of the respirator.

Among the six control animals which had artificial respiration only, and the eight which received intraventricular epinephrine also, one developed ventricular fibrillation and the rest showed no response whatever. The results for

TABLE 3.—*Procaine Hydrochloride Concentrations in Plasma Following Intravenous Injection*

Dose procaine HCl mg./Kg.	Minutes after injection	No. dogs	Procaine HCl mg./L. plasma, mean and S.D.
4	3	4	4.2 ± 1.2
	6	4	3.2 ± 0.7
	9	10	2.0 ± 0.5
8	3	8	7.1 ± 2.2
	6	8	6.8 ± 1.2
	9	10	4.4 ± 0.7
16	3	9	17.4 ± 5.2
32	3	3	19.4 ± 1.9

TABLE 4.—*Influence of State of the Arrested Heart on Results of Resuscitation Experiments*

Quality of arrest	No. "Resuscitations"	No. "Survivals"	No. failures	No. fibrillations
Complete	2	38	3	5
Persistent ECG	2	15	0	4
ECG and twitches	1	18	0	3
Totals	5	71	3	12

the 91 dogs in which an injection of one of the resuscitating drugs was combined with the use of artificial respiration and manual compression are summarized in table 5. The average mean arterial pressures and mean massage times for each of the agents are detailed in table 6.

Eighteen of the 24 animals injected with isotonic salt solution were "survivals" while an additional one was a "resuscitation." Ventricular fibrillation occurred during massage in four animals, and one failed to respond. The mean arterial pressure maintained by manual compression in the "revivals" was 35 (S.E. = 1.60) mm. Hg. The duration of massage before return of adequate cardiac function was 5.1 (S.E. = 1.44) minutes. (Massage time reached 27 minutes in one survival.)

Among the epinephrine-treated animals, 15 "survived," one was "resuscitated," and ventricular fibrillation developed in one. Cardiac massage produced a mean arterial pressure of 79 (S.E. = 6.2) mm. in the "revivals"; average massage duration was 0.8 (S.E. = 0.10) minutes.

Of 15 animals treated with norepinephrine, 12 "survived," two more were "resuscitated,' and ventricular fibrillation supervened in one. The average mean arterial pressure of massage in the "revivals" was 64 (S.E. = 4.3) mm. while the time to resumption of effective heart action was 1.1 (S.E. = 0.21) minutes.

When phenylephrine was used as the stimulant drug, "survivals" were noted in 13 experiments, "resuscitation" in one, and ventricular fibrillation in three. Manual compression gave a mean arterial pressure of 56 (S.E. = 2.8) mm. Hg, and the average duration of manual compression was 1.3 (S.E. = 0.24) minutes.

The acetylstrophanthidin-treated group showed 13 "survivals," three cases of ventricular fibrillations, and two completely unresponsive animals. The average mean arterial pressure during massage was 51 (S.E. = 3.2) mm. Hg for the "revivals," and heart action was effective in an average of 2.6 (S.E. = 0.32) minutes after resuscitative measures were initiated.

Chi-square analyses revealed no over-all differences in resuscitation and survival rates regardless of the agent or route. Table 6, however, shows a number of significant differences among the agents in the blood pressure and in the duration of manual compression. In all, epinephrine appeared the most effective of the drugs in promoting a higher arterial pressure during massage and in hastening the early return of heart action, while sodium chloride solution was the poorest. Complete failure of response was noted only after saline and acetylstrophanthidin. This suggests that stimulation of the circulation by rapidly acting sympathomimetic amines may have some value in cardiac resuscitation.

Although it has been reported that procaine depresses cardiac irritability,[5, 24–26] administration of extremely large doses intravenously in this study produced ventricular fibrillation in 8 of 10 dogs during pentobarbital anesthesia. A myocardial depressant action of ether has

TABLE 5.—*Results of Resuscitation and Survival Experiments*

Route	Range of total dose procaine hydrochloride causing arrest mg./Kg.	No. dogs tested	Complete arrests	Persistent ECG's	ECG's and twitches	"Survivals"	"Resuscitations"	Fibrillations	No response	Revivals attempts
0.9% NaCl Solution (2 ml.)										
Vein	4–60	8	3	5	0	5	1	2	0	6/8
Auricle	12–60	8	4	2	2	5	0	2	1	5/8
Ventricle	12–28	8	6	1	1	8	0	0	0	8/8
Totals		24	13	8	3	18	1	4	1	19/24
Epinephrine HCl (0.05 mg./Kg.)										
Vein	12–60	7	4	1	2	6	0	1	0	6/7
Auricle	12–60	5	2	1	2	4	1	0	0	5/5
Ventricle	12–28	5	3	1	1	5	0	0	0	5/5
Totals		17	9	3	5	15	1	1	0	16/17
***l*-Norepinephrine HCl (0.02 mg./Kg.)**										
Vein	12–28	5	3	1	1	4	1	0	0	5/5
Auricle	12–60	5	2	1	2	5	0	0	0	5/5
Ventricle	28–60	5	3	2	0	3	1	1	0	4/5
Totals		15	8	4	3	12	2	1	0	14/15
Phenylephrine (0.2 mg./Kg.)										
Vein	12–60	6	3	2	1	5	0	1	0	5/6
Auricle	12–60	7	6	0	1	5	1	1	0	6/7
Ventricle	28	4	3	0	1	3	0	1	0	3/4
Totals		17	12	2	3	13	1	3	0	14/17
Acetylstrophanthidin (0.1 mg./Kg.)										
Vein	12–28	5	3	1	1	4	0	0	1	4/5
Auricle	12–60	6	2	2	2	5	0	1	0	5/6
Ventricle	12–28	7	1	1	5	4	0	2	1	4/7
Totals		18	6	4	8	13	0	3	2	13/18
Totals by route										
Vein	4–60	31	16	10	5	24	2	4	1	26/31
Auricle	12–60	31	16	6	9	24	2	4	1	26/31
Ventricle	12–60	29	16	5	8	23	1	4	1	24/29
Grand Totals		91	48	21	22	71	5	12	3	76/91

also been demonstrated[29]; but ventricular fibrillation also followed directly on the injection of procaine in three ether-anesthetized animals (table 1). Furthermore, some of the hearts were sufficiently irritable during the resuscitation period so that fibrillation developed in 12 cases (table 5). By the time cardiac arrest was established in these studies, hypoxia of moderate to severe degree was present. The extent to which this may have

TABLE 6.—*Mean Arterial Pressures and Periods of Massage with the Various Resuscitating Drugs, and Their Differences*

Resuscitating Drug	Average Value ± S.E.	No. of dogs*	Differences/p of differences			
			Epinephrine	Norepinephrine	Phenylephrine	Acetyl strophanthidin
Mean Arterial Pressures (mm. Hg)						
Epinephrine	79 ± 6.18	15		15/>0.05	23/<0.01	28/<0.01
Norepinephrine	64 ± 4.27	14			8/>0.1	13/<0.05
Phenylephrine	56 ± 2.76	13				5/>0.2
Acetyl strophanthidin	51 ± 3.17	12				
Isotonic saline	35 ± 1.60	19	44/<0.01	29/<0.01	21/<0.01	16/<0.01
Massage Times (Minutes)						
Isotonic saline	5.1 ± 1.44	19	4.3/<0.01	4.0/<0.05	3.8/<0.05	2.5/>0.1
Acetyl strophanthidin	2.6 ± 0.32	12				
Phenylephrine	1.3 ± 0.24	13				1.3/<0.01
Norepinephrine	1.1 ± 0.21	14			0.2/>0.5	1.5/<0.01
Epinephrine	0.8 ± 0.10	15		0.3/>0.05	0.5/>0.5	1.8/<0.01

* Three less animals appear here than in table 5 because of unreadable kymograph recordings.

conditioned the fibrillatory response is uncertain.

DISCUSSION

The cardiac status which was accepted as arrest in these experiments was variable. The 24 cases in which the animals showed persistent electrocardiographic complexes without any myocardial movement may properly be called complete arrest since the condition of the heart muscle was such that it was not responsive to impulses which in some instances produced fairly normal electrocardiograms. In the 29 experiments in which both electrocardiograms and minimal nonfibrillatory movements of small areas of the ventricle were seen, there were no indications of peripheral movement of blood in that there was no pulsation in major arteries, no movement in the glass arterial cannula, and no oscillation in the mercury manometer. It is apparent, also, that "revival" rates were not influenced by these differences in cardiac state (table 4). The occurrence of electrocardiographic complexes was not a reliable index of the presence of effective ventricular contractions. Further support for this thesis is provided by the 14 control studies (artificial respiration alone or combined with intraventricular epinephrine) in which none of the animals was resuscitated, although two showed persistent ventricular complexes in the electrocardiogram and two showed myocardial twitches in addition. Previous reports have described agonal cardiac contractions. Negovsky,[12] who produced cardiovascular failure by hemorrhage, found them of no consequence; while Danielopolu and Marcou,[10] who used overdoses of chloroform as an arresting agent, stated that such movements in the heart muscle facilitated resuscitation by epinephrine. In agreement with Negovsky, we found this myocardial activity of no moment.

Since these cardiac arrests were produced under uniform conditions, and since the arrested hearts all responded similarly to resuscitative measures, a comparison of the various drugs or of the routes of injection is felt to be valid. Massage of the heart and artificial respiration were essential to revival. Furthermore, no great superiority was demonstrated for any resuscitative drug or route of administration (table 5). Our impression was, nevertheless, that higher massage blood pressures after epinephrine, norepinephrine and phenylephrine (table 6) were reflected by an increase in the palpable firmness of the heart.

The frequent resumption of an effective heart beat with such an increase in cardiac "tone" is in agreement with the findings of Wégria

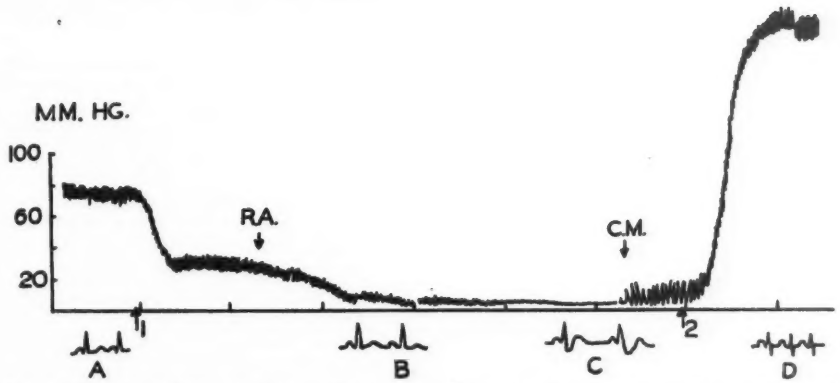

FIG. 1. Representative record of cardiac arrest and resuscitation. At 1, procaine hydrochloride, 16 mg per kilogram, was injected. One minute and 22 seconds later at R.A., respiratory arrest occurred. Within less than one minute, blood pressure was below 15 mm. Hg. Two and one-half minutes later all external evidence of heart action was gone and the chest was opened. The heart was found quiescent, but the electrocardiogram persisted. (Slight movement on kymograph tracing is attributable to manipulation of the dog during observation period.) At C.M. manual compression of the heart was begun; at 2, epinephrine, 0.05 mg. per kilogram was injected intravenously. Recovery of spontaneous heart action occurred rapidly, and the animal was sacrificed after 48 hours.

Electrocardiograms; *A*, control; normal sinus rhythm at 130 per minute. *B*, after respiratory arrest; sinus rhythm 100 per minute. *C*, abnormal electrocardiogram; apparently sinus rhythm, at 80 per minute, when the heart was quiescent. *D*, sinus rhythm at 195 per minute, immediately after resuscitation.

and his coworkers.[27] The observation that the strength of the returning beat may be suppressed by continuing massage confirms an earlier report by Gunn.[28] When any myocardial activity was detected, it was necessary to stop the manual manipulation of the heart in order to estimate the time of return of spontaneous cardiac action.

Our study did not indicate any superiority of intracardiac as compared with intravenous injections; and the direct stimulation of a flagging heart by needle puncture or by high local concentration of drug may be undesirable. If cardiac stimulating drugs are used, it is perhaps better to choose the more conservative intravenous route.

The mechanism of cardiovascular collapse following ether and procaine is suggested in studies of Brewster and associates,[29] who showed that functional intactness of the sympathoadrenal system is essential to circulatory adequacy during ether anesthesia. In their work blocking of this system or its surgical interruption revealed a direct cardiodepressant effect of ether. Procaine has been reported to interfere with the function of the cardiac nerves and the vagus[30] and to block ganglionic transmission.[31, 32] The cardiac arrest here reported may have resulted from diminution or abolition of reflex control of the heart, or from unmasking the depressant action of ether by procaine blockade of the adrenal medulla, or from a combination of these two effects. Hypoxia and depression of cardiac irritability and/or contractility may also have contributed.

CONCLUSIONS

1. A method of producing cardiac arrest by procaine during ether anesthesia has been described, and its mechanism postulated.

2. The nature of arrest was variable; but the presence of agonal contractions of the myocardium or of electrocardiographic change did not improve the probability of resuscitation.

3. Ventricular complexes in the electrocardiogram were found to persist in the absence of observable myocardial contractions in approximately 25 per cent of the animals.

4. When manual compression of the heart was not used, no resuscitations were observed.

5. Although massage blood pressures were higher and massage times were shorter when

epinephrine, norepinephrine or phenylephrine were used in resuscitation than after acetylstrophanthidin or isotonic salt solution, no differences in resuscitation or survival rates were demonstrated for any agent or route of administration.

6. An over-all resuscitation rate of 84 per cent was achieved.

Conclusiones in Interlingua

1. Es describite un methodo pro producer arresto cardiac per medio de procaina durante anesthesia a ethere. Le mechanismo del processo involvite es describite.

2. In le casos observate le arresto esseva variabile, sed le presentia de contractiones agonal del myocardio o de cambiamentos electrocardiographic non meliorava le probabilitate de resuscitation.

3. In circa 25 pro cento del animales complexos ventricular del electrocardiogramma persisteva in le absentia de observabile contractiones myocardial.

4. Sin uso de compression manual del corde nulle resuscitation esseva observate.

5. Ben que pressiones sanguinee a massage esseva plus alte e tempores de massage plus breve in casos ubi epinephrina, norepinephrina, o phenylephrina esseva usate in le resuscitation que in casos ubi acetylstrophanthidina o solutiones isotonic de sal esseva usate, nulle differentias del procentages de resuscitation o de superviventia esseva associabile con un o altere agente o con un o altere via de administration.

6. Esseva attingite un total de 84 pro cento de resuscitationes.

Acknowledgments

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A Study of the Ultraviolet Microscopy of Renal Vascular Diseases

By Sheldon C. Sommers, M.D., Ruth Crozier, M.A., and Shields Warren, M.D.

Newer methods of microscopy promise to provide a better insight into the physicochemical aspects of tissue structure than has been attained by conventional technics. An exploratory investigation is reported of the ultraviolet absorptive behavior of renal arterioles and arteries, employing the Polaroid color-translating ultraviolet microscope. In the arteriolar necrosis accompanying malignant hypertension and renal periarteritis nodosa changes of particular interest were observed.

In recent years pathologists have applied many new tools to the analysis of tissue changes in kidney disease. Histochemistry,[1-6] microspectrography,[7] phase contrast microscopy,[8] ultraviolet microscopy[9] and electron microscopy[3, 10] have yielded new evidence to support or refute traditional ideas of the morphologic bases of various kidney lesions. Another new technic, which permits color photomicrography in ultraviolet light, has recently become available. The Polaroid color-translating ultraviolet microscope allows the operator to choose any three wave lengths in the range of 2330 to 4000 Angstrom units, and to obtain accurately focused photomicrographs on 35 mm. film of tissues and other material, with each of the three wavelengths translated into a different color; blue, green and red. In the machine are a rapid film processor and a projector which superimposes the three images into a single colored picture.[11, 12] As many as 40 or more fields can be photographed in one work day. The range of wavelengths studied includes those at which proteins and nucleoproteins demonstrate peak absorptions, such as at approximately 2630 Angstrom units for nucleoproteins.

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To investigate whether stromal tissues had any peculiarities of ultraviolet absorption, an inquiry into the properties of normal and abnormal human and animal kidney tissues was undertaken. Kidney was chosen because it proved easy to identify its histologic components with the optical telescope and green-black contrasting appearances of unstained tissue used in the Polaroid instrument, which has green light for preliminary visual survey of the slide.

A rather surprising variation in the ultraviolet absorptions of glomeruli from different human kidney diseases was observed and is being reported elsewhere.[13] The absorption behavior was uniform between different slides, different kidneys and different persons with the same pathologic condition. In the case of persons with diabetes mellitus, the changes of glomerular stroma were considered distinctive enough to be diagnostic by ultraviolet photomicrography, in the presence or absence of identifiable pathologic alterations by ordinary pathologic criteria.

In the present communication the ultraviolet absorptive properties of arteries and arterioles in the same kidneys are considered.

Methods and Materials

As described previously, sections of paraffin-embedded kidney tissues were cut 4 μ or less thick, dry-mounted on Vycor slides, covered with glycerin after deparaffination with xylol, and Vycor cover glasses were then employed with a rim of paraffin. The tissues had either been Zenker-fixed and Autotechnicon-processed through to paraffin blocks, or had been frozen-dried and paraffin-embedded in vacuo. The design and operation of the Polaroid CTUV microscope are described elsewhere.[11, 12]

In each unstained slide studied, at ×2000 magnification on the projector screen, sufficient fields were examined to exclude possible local variations in tissue absorptions as a significant factor. More than one slide and case of each disease were used, up to the limitations of available time and adequate materials.

Human kidney diseases studied included cases of benign arterionephrosclerosis, malignant arteriolar nephrosclerosis, intercapillary glomerulosclerosis (Kimmelstiel-Wilson) in diabetes mellitus, chronic pyelonephritis, proliferative glomerulonephritis, amyloidosis, lupus erythematosus and periarteritis nodosa.

Each slide was studied at three sets of wavelengths:

Set 1	280, 263, 240 mμ
2	280, 263, 248
3	248, 240, 235

In each instance blue was used for the longest, green for the intermediate, and red for the shortest wavelength. The photographs taken would permit densitometry studies and plotting of absorption curves in the range 2800 to 2350 Ångstrom units.

Following ultraviolet photomicrography, the slides used were stained with hematoxylin and eosin, Masson-Goldner trichrome, Mallory aniline blue, or other special stains. The pathologic diagnosis was again confirmed using ordinary criteria. Often the same areas studied in ultraviolet light were scrutinized and compared with the ultraviolet photomicrographs. Aside from color projection of the 35 mm. film strips, black-and-white photographic prints and water-color paintings of some fields were available for review.

Results

The normal collagenous stromal components of a variety of tissues in humans and animals have a quite uniform ultraviolet absorptive behavior. The same ultraviolet absorptive properties characterized normal glomerular stroma. Zenker fixation had not altered relative color values, but produced hard bright colors instead of the soft pastels seen in frozen-dried tissue. Some nuclei were rendered opaque by chromation. In set 1 colors translated as pink to red violet, in set 2 violet, and in set 3 from red-orange to brown. In contrast to the wide variations in ultraviolet absorptions of diseased glomeruli observed,[13] the color translated appearance of normal or diseased arteries and arterioles proved quite uniform (table 1).

Both arteries and arterioles in the set 1 have red-pink to red-violet colors, in set 2 changing to violet or blue-gray. Sets 3 ranged from yellow-tan through orange-tan, olive-tan to brown. No distinctive color differences comparable to those observed in glomerular diseases were found in the arterioles or arteries studied. The elastica of arteries had absorptions differing from other elements: bright red in set 1, rose violet in set 2 and orange in set 3, contrasting respectively with red-violet, blue-violet and yellow-tan colors of muscle and stroma. This corresponded to greater absorption of elastica at shorter wavelengths.

The major disease processes showing distinctive arteriolar ultraviolet absorptions were those attended by arteriolar necrosis. Thus in malignant arteriolar nephrosclerosis and periarteritis nodosa, an unusual opacity to ultraviolet light was noted in all wavelengths tested. With color-translated projection the opaque areas appeared white or gray, indicative of greatly increased ultraviolet absorptions. The

Table 1—*Color-Translated Ultraviolet Absorptions of Arteries and Arterioles*

	Case	Field	Set 1 (280,263,240 mμ)	Set 2 (280,263,248 mμ)	Set 3 (248,240,235 mμ)
Normal	3	5	red-violet	gray-violet	yellow-brown
Diabetic nephropathy	3	4	red-violet	gray-violet	orange-tan
Chronic pyelonephritis; Arteriosclerosis	2	4	red-violet	gray-violet	tan-brown
Glomerulonephritis	1	1	red-violet	gray-violet	pink-tan
Amyloidosis	3	3	red-violet	blue-violet	yellow-tan
elastica			red	rose-violet	orange
Lupus erythematosus	2	2	pink-violet	red-violet	gray-tan
Malignant arteriolar nephrosclerosis	2	5	carmine	violet	yellow-gray
Arteriolar necrosis	1	3	white	—	—
4× exposure			white & carmine	—	—
8× exposure			carmine	—	—
Periarteritis nodosa	2	5	pink-violet	red-violet	gray-tan
elastica			red	violet	tan
arterial necrosis	1	5	—	—	gray
4× exposure			—	—	olive-tan
8× exposure			—	—	olive-brown

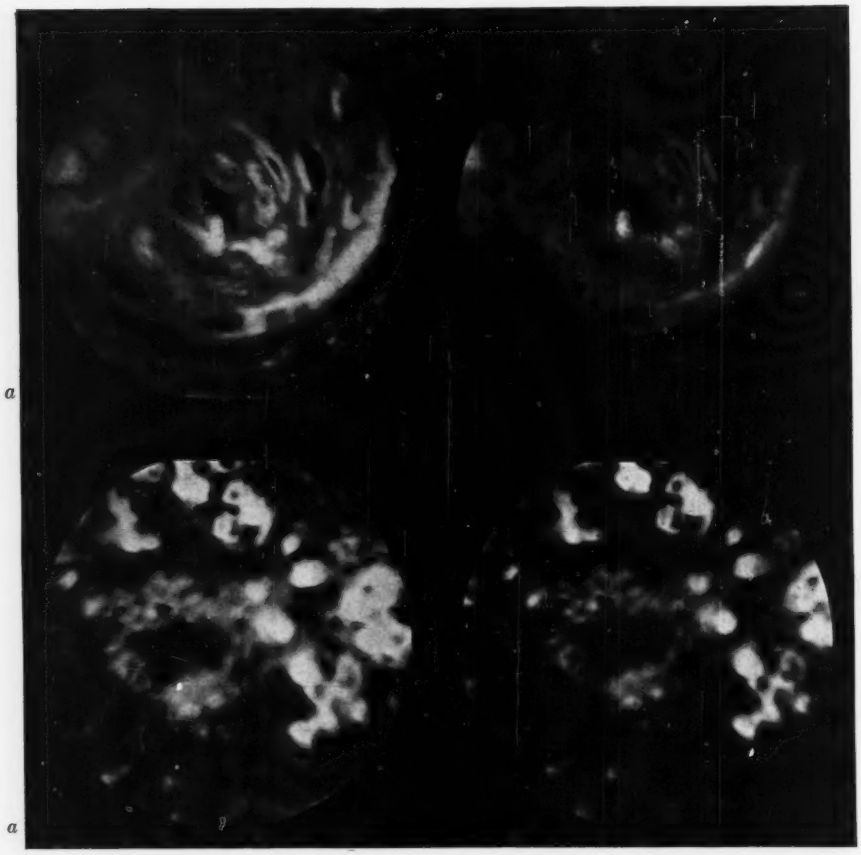

FIG. 1. (*a*) Arteriole from kidney of malignant nephrosclerosis, Zenker-fixed, demonstrating a focus of fibrinoid necrosis with abnormally increased ultraviolet absorption, translated as white. Set 1, 280, 263 and 240 mμ, normal photographic exposure. (×1000.) (*b*) The same field, set 1, photomicrography at eight times the normal photographic exposure. Ultraviolet absorption of the fibrinoid necrosis is altered toward normal.

FIG. 2. (*a*) Arteriole from renal periarteritis nodosa, Zenker-fixed. Necrosis of the wall has produced an increased ultraviolet absorption, indicated by the pale area. Set 3, 248, 240 and 235 mμ, normal photographic exposure. (×1000) (*b*) The same field as shown in figure 2*a*, set 3, photomicrography at twice usual exposure time. Absorptions now appear within normal limits.

only other components of tissues reacting similarly that have been studied included deposits of calcium or hemosiderin, and some nuclei which had been chromated by Zenker's solution. Photographic exposures of eight times the usual time interval resulted in the restoration of the colors usual for the arterioles investigated (figs. 1 and 2). This indicated that while ultraviolet absorption was markedly increased, absorptive properties were not apparently qualitatively altered.

Similar observations by microspectrography of increased ultraviolet absorptions at shorter wavelengths have been made in a study of arteriolar sclerosis and necrosis in human and animal tissues.[7]

As already mentioned, benign nephrosclerosis, chronic pyelonephritis and amyloidosis failed to demonstrate distinctly abnormal ultraviolet absorptions of arterioles and arteries (fig. 3).

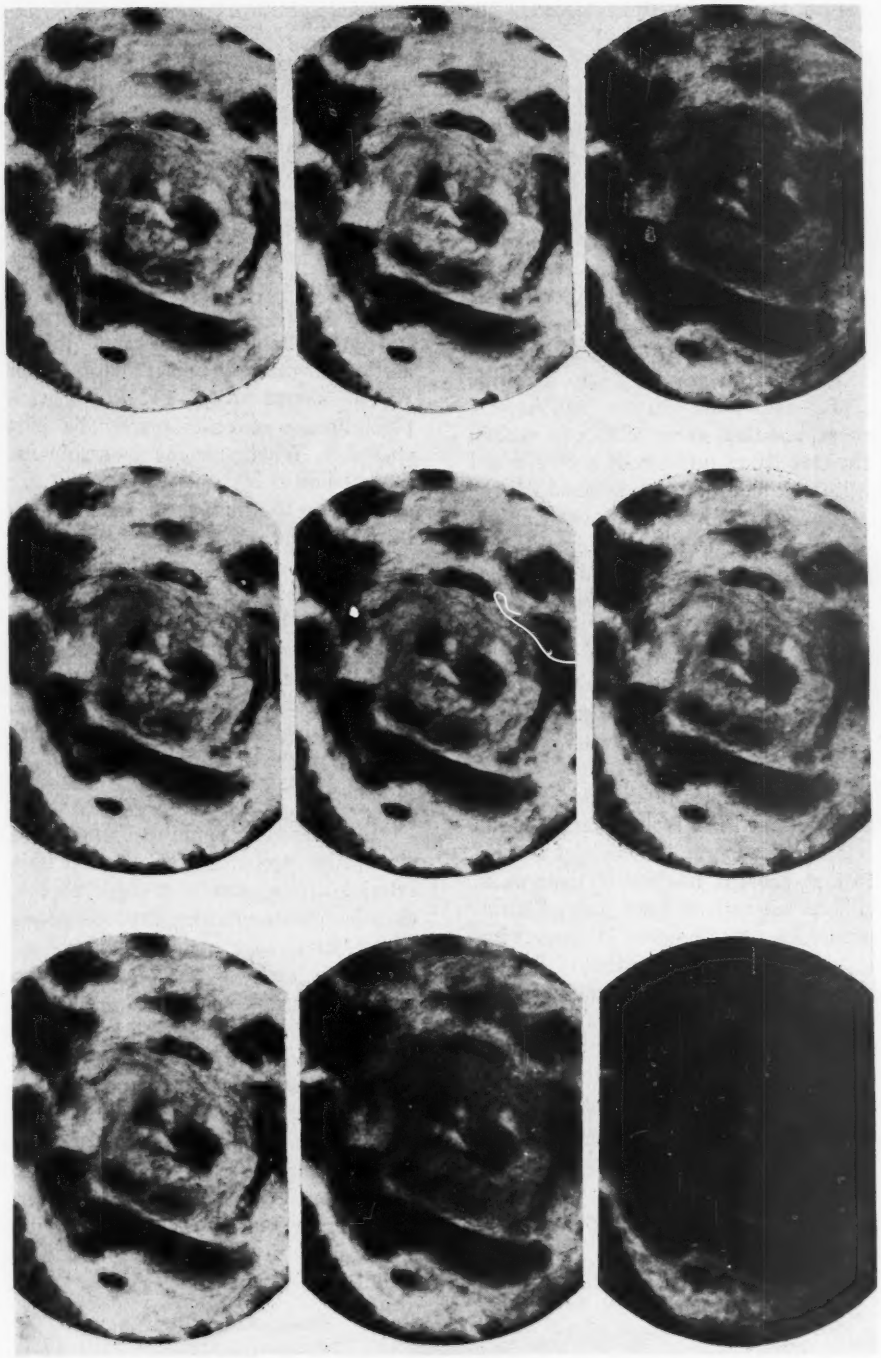

FIG. 3. Positive photographic prints of original 35 mm. film strip. Top horizontal row, set 1: left to right 280, 263 and 240 mμ; middle horizontal row, set 2: left to right 280, 263 and 248 mμ; bottom horizontal row, set 3: left to right 248, 240 and 235 mμ. Left-hand vertical rows are translated into blue, middle vertical rows into green, and right-hand vertical rows into red. Darker shades represent increased ultraviolet absorption. A sclerotic arteriole from a kidney with chronic pyelonephritis, frozen-dried, is shown. Absorptions are not significantly abnormal. (×1000.)

Discussion

Studies of tissue pathology using ultraviolet light over a considerable range of wavelengths are quite new. Many findings have been and will probably be unexpected, such as the distinctive differences observed in glomerular stromal absorptions in various clinically and pathologically identifiable glomerular diseases. Aside from concluding from the study of different blocks of kidney tissues from various patients that the observations were not due to localized peculiarities of certain areas of tissue, and were uniform for individual disease entities, no complete explanation was available to explain the ultraviolet absorptive behavior of diseased glomeruli. Biochemical observations of the ultraviolet absorption spectra of collagen during successive purification procedures which removed ground substances have shown similar changes in the same wavelength range as investigated in the present study.[14] This suggests that mixtures of partly denatured glomerular stromal proteins surrounded by abnormal amounts of normal or abnormal ground substances could be responsible for the observations.

Arteries and arterioles of diseased kidneys studied have proved less labile than glomeruli in demonstrating abnormal ultraviolet absorptions. In fact, short of necrosis of their walls, no significant alterations from normal ultraviolet properties were observed in various important kidney diseases. Despite definite morphologic changes in arterial walls in these conditions, ultraviolet absorptions were considered within normal limits.

Possible explanations suggested for the negative findings are (1) that the material was chosen particularly to study glomeruli and did not illustrate the most outspoken arterial and arteriolar lesions. However, there were striking vascular changes at least in the diabetic, amyloidosis and periarteritis nodosa material. (2) Despite histologic changes, the preponderance of normal smooth muscle and collagen still unaltered in most of the blood vessel walls perhaps obscured abnormalities in ultraviolet absorption. In glomeruli a significantly greater proportion of stroma was likely damaged, with resulting visibly altered ultraviolet properties.

The positive findings of greatly increased ultraviolet absorption, up to eight times normal, in the vascular necroses of malignant arteriolar nephrosclerosis and periarteritis nodosa were unexpected, since no such increased density is found with visible light. The normal ultraviolet absorptions of adjacent kidney tissues testified that this change was not attributable to increased thickness of sections or other technical factors. Apparently protein denaturation and coagulation with precipitation of colloids may be partly responsible. Whether some inorganic materials like calcium or iron also are attached to protein and add to the ultraviolet opacity remains to be determined.

Further studies with ultraviolet photomicrography of renal vascular diseases would appear promising. It would be of interest to investigate the effects of enzymes, hydrolyzing agents and salts upon the ultraviolet absorptive properties of vessel walls. Since the slides are examined unstained, later histochemical studies of the identical sections are feasible.

Summary

An exploratory study of the ultraviolet absorption properties of renal arteries and arterioles from cases of diabetic nephropathy, chronic pyelonephritis, arteriosclerosis, malignant arteriolar nephrosclerosis, glomerulonephritis, amyloidosis, lupus erythematosus, and periarteritis nodosa has been carried out with the Polaroid color-translating ultraviolet microscope. Unlike the distinctive alterations of ultraviolet absorptions found in diseased glomeruli, the arterial and arteriolar ultraviolet properties generally were unaltered. In the vascular necroses of arteriolar nephrosclerosis and periarteritis nodosa the ultraviolet absorptions of vessel walls were increased up to eight times normal. The basis of the findings is discussed.

Summario in Interlingua

Esseva executate per medio del polaroide microscopio ultraviolette coloritraducente un studio exploratori del qualitates de absorption

ultraviolette de arterias e arteriolas ab casos le nephropathia diabetic, pyelonephritis chronic, arteriosclerosis, maligne nephrosclerosis arteriolar, glomerulonephritis, amyloidosis, lupus erythematose, e periarteritis nodose. In contrasto con le alterationes characteristic del absorptiones ultraviolette observate in glomerulos morbide, le qualitates ultraviolette del arterias e arteriolas esseva generalmente intacte. In casos de necrosis vascular de nephrosclerosis arteriolar e de periarteritis nodose, le absorption ultraviolette del parietes vascular esseva augmentate usque a 8 vices le normal. Le base de iste constatationes es discutite.

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Effects of Acute Removal of Potassium from Dogs

Changes in the Electrocardiogram

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Potassium has been rapidly removed from the circulating blood of dogs in 22 experiments in which other extracellular electrolytes were maintained constant. In these experiments potassium extraction occurred in an acute phase accompanied by a reduction in serum level and a second phase of continued extraction with little change in the extracellular concentration. In the first phase the P wave increased markedly in amplitude and width. The A-V conduction time became prolonged. The QRS complex widened, the T wave became broadened and rounded, and the S-T segment depressed, the latter change occurring in the second phase of dialysis. In these experiments, acute depletion of potassium in dogs consistently reflects the electrocardiographic changes ascribed to hypokalemia.

RINGER clearly demonstrated by means of an isolated frog-heart preparation that the contraction of heart muscle was dependent on the electrolyte composition of the perfusing fluid.[1] Numerous investigators have confirmed these findings in animals and have extended the observations to include the associated alterations in the electrocardiogram.[2] However, until recently it has not been possible to remove a selected electrolyte quantitatively and rapidly from an intact animal and at the same time to maintain the relative constancy of other electrolytes. External hemodialysis permits such a procedure. This procedure has been applied to the removal of potassium from the circulating blood of dogs. This procedure permits the rapid removal of potassium from the extracellular fluid. In addition, our observations and those of Reinecke, Holland, and Stutzman[3] have shown that an amount of potassium could be removed by hemodialysis that was equal to or greater than that calculated to be present in the extracellular fluid of dogs.

The present study had the following three objectives: (1) to assess the rapidity and extent of potassium removal by hemodialysis, (2) to delineate the alterations in the electrocardiographic pattern following such removal, and (3) to attempt to determine the role of both cellular and extracellular potassium in these changes.

METHODS

Rapid removal or addition of potassium was carried out in dogs by means of a Kolff-type hemodialyzer ("artificial kidney"). The technical aspects of dialysis were similar to those previously described[4] except for the following modifications: (1) A flow of 100 to 300 ml. of blood per minute through the machine was obtained by cannulation of the femoral artery and vein. (2) The length of cellophane tubing was limited to 70 feet. (3) Prior to dialysis, the dead space in the machine was filled with 400 ml. of heparinized blood drawn from donor dogs. (4) The composition of the bath fluid, which approximated the electrolyte concentration of dog serum, was altered in these experiments only in respect to its potassium content. When potassium removal was begun, no potassium was present in the bath so that its concentration was nearly zero. When potassium addition was carried out, the concentration of

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potassium in the dialysate bath was raised to 8 mEq. per liter.

Twenty-two hemodialyses were carried out on 14 mongrel dogs of both sexes ranging in weight from 9 to 14 Kg. The dogs were maintained under pentobarbital or morphine anesthesia or analgesia during dialysis. These drugs were administered intravenously. The dosage schedule of pentobarbital was 30 mg. per kilogram initially and approximately 3 mg. per kilogram at hourly intervals. The initial morphine dose was 3 mg. per kilogram followed by approximately 1 mg. per kilogram every hour. Heparin was administered intravenously in a dose of 20 mg. at the start and then 5 mg. hourly. Electrocardiograms were taken with a direct-writing, amplifier-type electrocardiograph. Limb, unipolar, and chest leads, maintained at a constant position, were recorded at frequent intervals during dialysis. Observations on the arterial blood pressure were made by means of an aneroid manometer attached by tubing to a side-arm of the arterial cannula. In the majority of experiments the arterial blood pressure was well maintained throughout dialysis.

The 22 dialyses consisted of three groups of experiments. In 13 dialyses, referred to as group I, the dogs were subjected to no other procedure except potassium extraction for an average duration of 4 hours and 8 minutes. Group II consisted of seven dialyses of shorter duration having an average time of 1 hour and 23 minutes. In this group digitalization was carried out at the end of the period of potassium extraction to study the relation between digitalis toxicity and potassium. These studies will be reported later.[5] In two dogs the extraction of potassium was begun after the serum potassium concentration had been raised to 8 mEq. per liter. These dogs constitute group III. In dialyses in all groups after the completion of extraction, the serum potassium level was rapidly raised by dialyzing against a bath potassium of 8 mEq. per liter.

The amount of potassium removed was determined by measuring the increment in the potassium concentration of the bath fluid. Sodium and potassium were determined with a Barclay flame photometer using lithium as an internal standard; chloride was determined by the method of Schales and Schales,[6] and calcium by the method of Clark and Collip.[7]

Results

Rate of Potassium Transfer

During hemodialysis potassium is removed from the body if the concentration of potassium in the dialysate bath is lower than that in the plasma. In figure 1, the dotted line shows the rate of extraction of potassium when there is no potassium present in the bath. It can be seen that the removal of potassium from the body continues at a fairly constant rate throughout several hours of dialysis. The rate of potassium extraction averages nearly 10 mEq. per hour, although there is some variation between experiments probably due to variations in the rate of flow of blood through the machine, the total amount extracted being less with a low rate of flow of blood and greater with a high flow rate.

The effect of this rapid removal of potassium upon the concentration of potassium in the extracellular compartment is shown in figure 1 by the solid line. During the first hour of dialysis there is a rapid fall in the plasma potassium concentration. However, following this initial period of rapid lowering, the level of potassium in the plasma tends to become stabilized at about one-half of its original value. In these experiments continuation of dialysis beyond two hours did not result in any further decrease in the plasma potassium concentration which averages about 2 mEq. per liter. During this period potassium is continually being removed from the body. In a 10 Kg. dog with an assumed extracellular phase of 20 per cent of body weight (2 liters) a decrease in the extracellular potassium concentration from 4 to 2 mEq. per liter represents an extraction of only 4 mEq. of potassium from this phase. More than two and

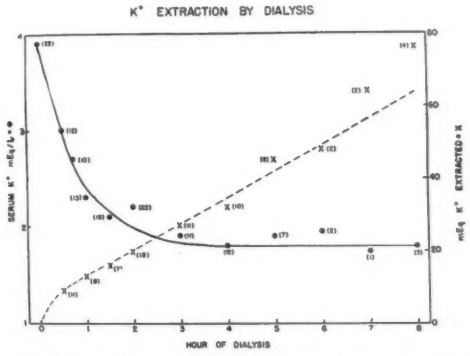

FIG. 1. Relation of the duration of hemodialysis to changes in the serum potassium concentration (solid circles) and the amount of potassium removed from the body (crosses). Figures in parenthesis represent number of determinations from which means have been calculated.

TABLE 1.—*Data on 22 Hemodialyses on 14 Dogs. The Incidence of Electrocardiographic Changes Is Related to the Duration of Dialysis and the Alterations in Potassium*

Group	No.	Hemodialysis Data					Electrocardiographic Changes							
		Duration of Dialysis (minutes)	Serum K^+ (mEq./L.)			Amount K^+ Extracted (mEq.)	Rate (beats/min.)		Increase in P-wave Height (1 mm.)	Prolonged P-R Interval (0.02 sec.)	QRS		Increase in T-wave area	Depression of S-T segment (0.05 mm.)
			Initial	Final	Decrease		Initial	Final			Widening	Shift in Axis		
I	13	248	3.8	1.9	1.9	36*	144	171	12	9	9	10	13	13
II	7	83	4.0	2.2	1.8	18	154	161	5	4	1	2	3	1
III	2	115	8.0	2.3	5.7	33	155	205	2	1	1	1	1	1

* Data from 11 dialyses.

one-half times this amount is usually removed during the first hour of dialysis. The difference must be derived from some other source than the extracellular compartment as must be all potassium which is extracted during the period when the plasma potassium is being maintained at a constant level. Because the content of potassium in the cellular compartment is large, about 2 per cent of the total amount of potassium in the cellular phase is being removed hourly. Cellular potassium is apparently transferred into the extracellular compartment at a rate sufficient to maintain the concentration of potassium in the extracellular phase at a nearly constant level.

Extraction of body potassium by this method of hemodialysis may, therefore, be considered as occurring in two phases: (1) A phase of rapid lowering (during the first hour) of the extracellular potassium concentration to one half of its initial value, and (2) a phase of continuing extraction occurring beyond the first hour during which time the potassium concentration in the extracellular compartment remains nearly constant. The potassium extracted during this phase is presumably derived from the cellular compartment.

Electrocardiographic Changes

The removal of potassium from the body induced changes both in auricular and ventricular components of the electrocardiogram. The incidence and type of alterations, as related to the quantity of potassium extracted, are shown in table 1.

The earliest electrocardiographic effect was an increase in the height and width of the P wave. There occurred a doubling, or at times even a tripling, in its amplitude. These changes were best observed in leads II, III, and aV_F. The alterations in P wave were associated with a prolongation of auriculoventricular conduction time. With continued removal of potassium, the P-R interval lengthened, the P wave "migrated" and eventually fused with the T wave (figs. 2–4). In some instances it emerged before the inception of the T complex (fig. 3). Increases in the duration of A-V conduction were noted only in conjunction with changes in the P wave. These alterations were

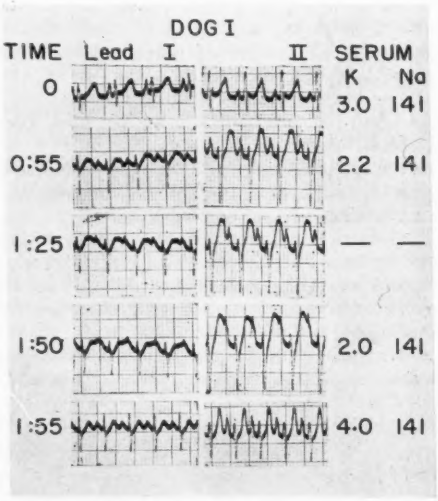

FIG. 2. Increase in P-wave amplitude, prolongation of P-R interval with fusion between the P and T waves occurring during the early phase of dialysis.

In this and subsequent figures, the length of dialysis in hours and minutes is indicated under time; the serum potassium and sodium concentrations are expressed in milliequivalents per liter, and the amount of potassium removed in milliequivalents.

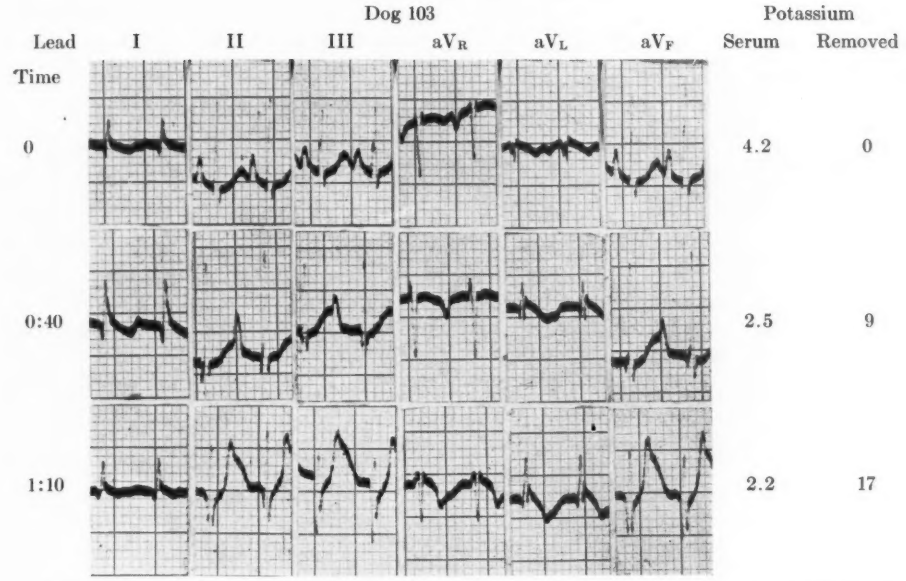

FIG. 3. Migration of P wave with its emergence before the inception of the T wave during the first 1 hour and 10 minutes of dialysis.

maximal during the first two hours of dialysis during the phase of rapid lowering of the extracellular potassium. In only one instance did the P wave continue to increase in size after the stabilization of the serum potassium level (fig. 6).

Significant augmentations of the heart rate resulted from the removal of body potassium. The increase in rate was a function of the duration of the extraction. In group I, rate accelerations of over 10 per cent occurred in 9 of the 13 hemodialyses, with an average increase of 27 beats per minute for the entire group. Similar degrees of acceleration were noted in only two of the seven hemodialyses in group II in which the increase averaged seven beats per minute (table 1). The increase in heart rate did not depend on changes in the P wave or P-R interval.

Widening of the QRS complex and shift in its axis were two common alterations in the ventricular component which attended the removal of potassium. Increase in the duration of the QRS was a notable feature only after the serum potassium level became fixed around 2.0 mEq. per liter. The so-called axis shift consisted of a diminution in the R wave in the standard leads and the emergence or increase in the amplitude of the S wave in leads II, III, aV_F, and the precordial leads. The heart shifted in its electrical position with a counterclockwise rotation on the anteroposterior axis and clockwise rotation on the longitudinal axis (figs. 4 and 6). The vector projection of ventricular depolarization thus became directed toward the left upper limb and posteriorly. These changes began early and evolved throughout the entire dialysis.

T-wave changes were difficult to study because of the rapid heart rates and the superposition of the P wave on the T wave. This also prevented determination of changes in the Q-T interval. In those instances where P- and T-wave fusion did not occur, there was no alteration in the T-wave direction. Generally the T wave widened, increased in amplitude and assumed a rounded contour. Often it exhibited a small degree of notching at its apex. This may have been due to the incorporation of a U wave. Changes in the T wave began early in dialysis and were complete

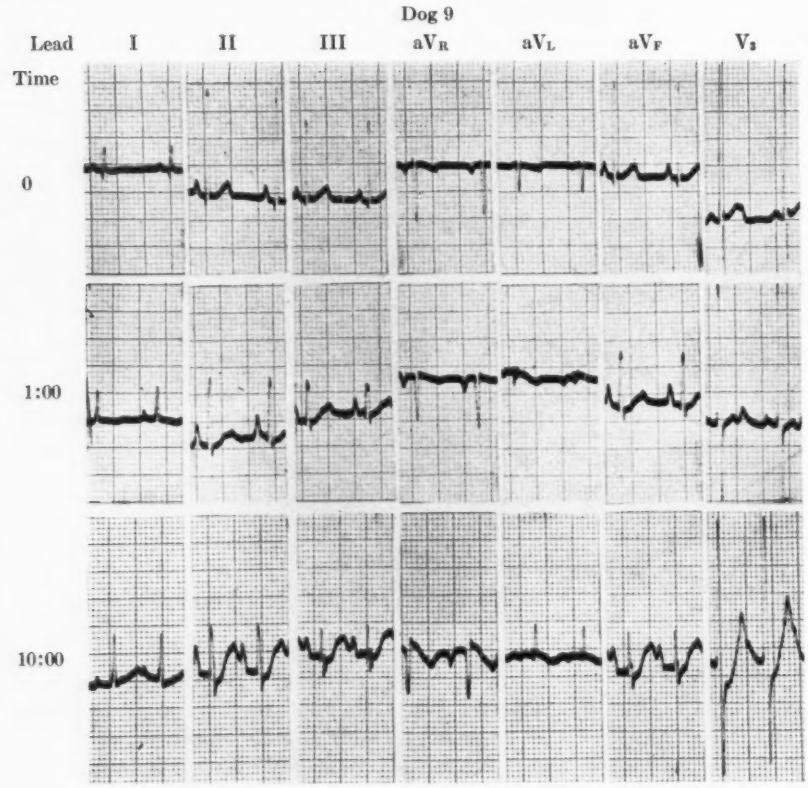

FIG. 4. Acceleration of heart rate, fusion of P and T waves, shift in QRS axis, as well as depression of S-T segment occurring during extensive depletion of potassium.

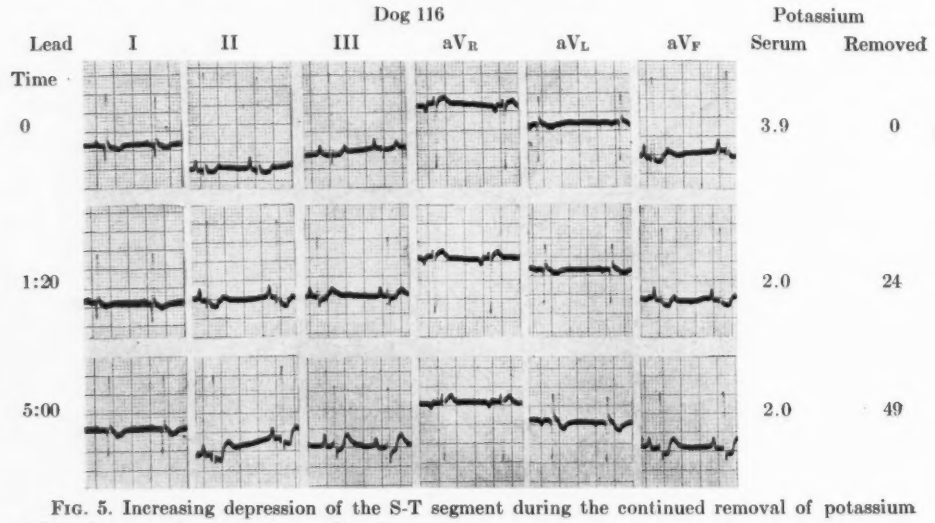

FIG. 5. Increasing depression of the S-T segment during the continued removal of potassium while the serum level remains unaltered.

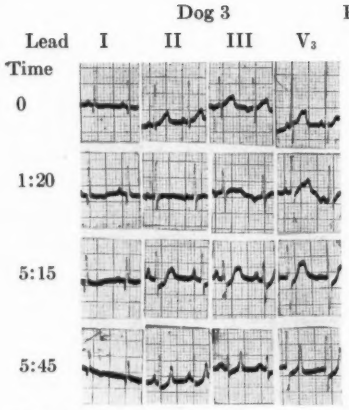

FIG. 6. Depression of S-T segment occurring after stabilization of serum potassium concentration, with a failure to return to the base line even after induction of severe degree of hyperkalemia.

usually at the time the lowest serum potassium level was achieved.

Significant depression of the S-T segment occurred during the phase of slow removal of potassium, at a time when the serum level remained fixed. The degree of depression appeared to relate to the amount of potassium extracted from the body. When the serum potassium was restored to its predialysis level all electrocardiographic parameters, except for the S-T segment, rapidly reverted to normal. Even after the serum potassium level was rapidly raised to 11.2 mEq. per liter, the S-T segment depression persisted (fig. 6).

Ten of the 14 dogs in this study were subjected to additional dialyses during which the potassium ion concentration in the bath fluid was kept constant. These hemodialyses against normal baths were carried out for a minimum of eight hours. In no instance were any of the electrocardiographic effects of potassium removal noted. The sole results were occasional nonspecific alterations in the T wave.

Electrocardiographic changes resulting from potassium extraction can be classified into one of three groups: (1) Changes limited to the phase of rapid serum potassium decline, which consisted of increases in the amplitude of the P wave, widening and rounding of the T wave and prolongation of the P-R interval; (2) changes taking place throughout the process of potassium removal, which consisted of shifts in the QRS axis and acceleration of heart rate; (3) changes occurring during the phase of continuing extraction of potassium during which time the serum level remains fixed; these consisted of depression of the S-T segment and widening of the QRS complex.

DISCUSSION

The rate of blood flow through the artificial kidney and the concentration of potassium in the bath fluid determine the rapidity with which this ion is removed from the body. Under the conditions of these experiments it was not possible to reduce the serum potassium concentration much below 2.0 mEq. per liter, with a blood flow through the apparatus ranging from 100 to 300 cc. per minute and with frequent changes of the bath fluid so as to maintain bath potassium close to zero. After this serum level was achieved, the extracellular space apparently served merely as a conduit for the transport and removal of body potassium. In those instances where technical factors caused temporary cessation of dialysis, there was a prompt rise in the serum concentration. It is of interest that patients who sustain massive potassium losses seldom exhibit serum potassium values of less than 2.0 mEq. per liter. When the organism is depleted of potassium, it appears that mechanisms are activated within the cellular compartments to defend the extracellular potassium concentration. The potassium level reached in these experiments represents an equilibrium between extracellular extraction and cellular restitution. What conditions equilibration at about 50 per cent of the initial serum value is unknown. No doubt the rapidity of extraction as well as its duration are factors.

Extensive potassium depletion in human beings gives rise to distinctive electrocardiographic changes. The effects predominantly involve the process of ventricular repolarization. The S-T segment becomes depressed, the T wave becomes flattened and inverted with emergence and prominence of the U wave. The duration of the Q-T interval remains un-

altered.[8] No similar T- or U-wave alterations were distinguishable in this study. This is attributable to the rapid heart rate, increased prominence of the P waves, and prolongation of the P-R interval which accompanied the removal of potassium. Attention has been drawn to the fact that similar alterations interfere with the electrocardiographic recognition of hypokalemia in patients.[9]

In advanced hyperkalemia, there is diminution of the P wave eventuating in auricular standstill. The converse changes in the auricular complex during potassium depletion have not been emphasized to date. Prominence of the P wave was noted in dog experiments in which the serum potassium concentration was lowered by the infusion of sodium bicarbonate.[10]

Peaked P waves have been observed in patients with hypokalemia due to diabetic acidosis.[11, 12] Others have also commented upon the occurrence of A-V conduction disturbances[13, 14] as well as ectopic auricular rhythms in association with hypokalemia.[8, 15, 16] Surawicz and Lepeschkin found the P waves to be taller at the height of hypopotassemia in all of their eight patients who experienced losses of potassium.[8] Three of these patients demonstrated, in addition, prolongations of the P-R interval. These investigators believe that peaked P waves, A-V conduction impairments and ectopic rhythms are useful as corroborative evidence of hypokalemia when other electrocardiographic criteria are equivocal.[8]

These auricular changes shed light on the genesis of one of the arrhythmias encountered in patients with congestive heart failure. Lown and co-workers have demonstrated that, in the presence of potassium deficits, digitalis will precipitate ectopic auricular mechanisms. The prototype of these arrhythmias is paroxysmal auricular tachycardia with block.[17, 18] When digitalis is administered in the presence of potassium depletion, there occurs an acceleration of pacemaker, changes in the P wave and varying degrees of A-V block. It has been demonstrated that digitalis in overdose induces loss of myocardial potassium.[19, 20] These abnormal mechanisms may, therefore, be the result of accentuation by digitalis of existing potassium deficits within the myocardium.

In a recent study no correlation was found between the electrocardiogram and the serum potassium concentration or the cumulative potassium balance.[21] These studies concerned for the most part moderate degrees of chronic potassium depletion produced experimentally in previously normal subjects. Such absence of correlation is not surprising. The electrocardiogram reflects directly only intracardiac events. It seems unlikely that all organs participate to the same degree when a deficit of potassium is chronically incurred. The varying metabolic activity of different tissues is known to effect the transfer of cations. The cellular compartment is not a homogeneous reservoir. "Factors governing the concentration of the bulk ions no doubt are differentiated to subserve specific tissue function and thus concentration will vary from tissue to tissue with changes in external and internal environment."[18] Thus, if the myocardium does not participate in the potassium loss, no changes will ensue in the electrocardiogram, irrespective of the extent of the depletion. It has been our experience that in many patients with severe heart disease, acute though minor shifts in body potassium resulted in full blown hypokalemic electrocardiogram. The critical difference appears to be the rate at which such deficits have occurred.

The present study suggests the participation of acute cellular potassium depletion in the effect upon the hypokalemic electrocardiogram. Sequential changes in the electrocardiogram continued during the extraction of body potassium at a time when the serum potassium concentration remained unaltered. This was especially evident in the changes of the S-T segment. Not only was there a delay in the depression of the S-T segment during dialysis, but its return to the base line was also delayed upon restoration of the serum potassium level to the predialysis concentration. Presumably there is a lag in the correction of cellular deficits, and this was reflected in the electrocardiogram.

Conclusions

1. The removal of potassium was accomplished by means of hemodialysis 22 times in 14 dogs. Other extracellular electrolytes were maintained at predialysis concentrations. Electrocardiograms were taken during the removal of potassium and following restoration of the serum level to its predialysis value.

2. Potassium extraction occurred in two phases: a phase of rapid reduction of the serum level to 2 mEq. per liter, followed by a phase of continued extraction of body potassium with the extracellular concentration remaining fixed.

3. Striking changes were observed in the P wave, consisting of increases in amplitude and width. A-V conduction time became prolonged and the heart rate was accelerated. These alterations occurred in the first phase of dialysis during the period of rapidly developing hypokalemia.

4. Ventricular changes consisted of a widening in the QRS, a shift in its axis, broadening and rounding of the T wave and depression of the S-T segment. Changes in the S-T segment occurred in the second phase of dialysis during which time the serum potassium level remained stable.

5. This study suggests that acute depletion of potassium faithfully contributes to the electrocardiographic picture of hypokalemia.

Conclusiones in Interlingua

1. Per medio de hemodialyse le suppression de kalium esseva effectuate in 14 canes a 22 occasiones. Altere electrolytos extracellular esseva mantenite al concentrationes predialytic. Electrocardiogrammas esseva facite durante le suppression del kalium e post le restauration del nivello seral a su valores predialytic.

2. Le extraction de kalium occurreva in duo phases: un phase de rapide reduction del nivello seral a 2 mEq sequite per un phase de continuate extraction de kalium del corpore durante que le concentration extracellular remaneva constante.

3. Esseva observate frappante cambiamentos in le unda P. Istos consisteva de augmentos de amplitude e largor. Le tempore de conduction A-V esseva prolongate e le frequentia cardiac esseva accelerate. Iste cambiamentos occurreva intra le prime phase del dialyse durante le periodo del rapide disveloppamento de hypokalemia.

4. Cambiamentos ventricular consisteva in un allargamento de QRS, un transposition de su axe, un extension lateral e un rotendification del unda T, e le depression del segmento S-T. Cambiamentos del segmento S-T occurreva in le curso del secunde phase dialytic, i.e. durante le tempore quando le nivello del kalium seral remaneva constante.

5. Iste studio suggere que un acute depletion de kalium contribue invariabilemente al configuration electrocardiographic characteristic de hypokalemia.

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The Changing Electrocardiogram in Wilson Block*

By CORNELIO PAPP, M.D. AND K. SHIRLEY SMITH, F.R.C.P.

The significance of the Wilson variety of right bundle-branch block was investigated on the basis of serial electrocardiographic changes seen in almost half of the series. Wilson block may originate from both anteroseptal and posterior infarction; in the former it may form a solitary relic without prognostic significance; in the latter it denotes extensive septal involvement. It may modify the injury pattern of anterior infarction and may abolish the signs of posterior infarction; cardiac infarction may approximate it to the classic form of right bundle-branch block. Except in two patients, less than 4 per cent of the series, it was related to pathologic causes; it should therefore be regarded as a sign of organic heart disease.

RIGHT bundle-branch block has of late years lost much of the sinister reputation which it used to have, and which still attaches to left bundle-branch block. Numerous authors have emphasised the harmlessness of the variety of right bundle-branch disorder first defined by Wilson, Johnston, Hill, Macleod and Barker[1] in 1934. Bundle-branch block, whether right or left, is often regarded as a stable electrocardiographic pattern and we have been surprised to find that in almost half of our patients showing the Wilson type of right bundle-branch block, the record has at one time or another changed. It seemed likely that a study of such serial changes might help to solve some of the problems connected with this disorder of conduction, especially its relation to coronary disease. In this paper, we present the results of a review of 53 patients showing the Wilson pattern of right bundle-branch block. In particular, we have sought to establish the diagnostic and prognostic meaning of changes in the electrocardiogram in this condition, and to emphasise the fact that only rarely is it without morbid significance.

Long before it was proved to be due to right bundle-branch block, Oppenheimer, Rothschild and Mann[2] emphasised the good prognosis in a special form of intraventricular block where the widening and notching of the ventricular complex was "entirely confined to the terminal portion of the second limb of the R wave." Their impression, gained in 10 patients, was reaffirmed by Van Desten and Dolganos,[3] and has been since endorsed in a number of papers.

In Wood, Jeffers and Wolferth's[4] series of 64 patients showing this pattern, only 29 had definite signs of heart disease. In the largest series ever published, that of Dry, Willius and Reeser,[5] only 22 per cent of 492 cases had angina or congestive heart failure when the lesion was discovered. Although most of these patients were in the arteriosclerotic age group, 62 lived 10 years or more. There was a high mortality of 20 per cent during the first year because of the association with cardiac infarction, but after this, the life expectancy curve tended to parallel that of the normal population.[6] These authors advocated a separate group for the "wide S" variety of bundle-branch block because of its relatively benign significance when "unattended by coexistent findings indicative of organic heart disease." Similar conclusions were reached by Perera, Levine and Erlanger[7] and by Schulze,[8] who also denied the prognostic significance hitherto attached by Franke[9] to the width of the S-wave. Out of a series of 281 patients observed by Shreenivas, Messer, John-

From the Cardiac Department of Charing Cross Hospital and of the London Chest Hospital, and the private files of the authors.

* The wide S wave pattern of bundle branch block[5, 6] is here called Wilson block. This term is used to acknowledge the debt we all owe to Frank N. Wilson who with his associates first studied this electrocardiographic pattern which he was able to reproduce in dogs by section of the right branch of the bundle[1]—and to substitute for an eight word description a two word designation. The term Wilson block in this context has been in common use in Europe for many years[8, 20].

son and White,[10] 27 per cent lived longer than five years; but this proportion rose to 39 per cent in 186 patients who could be traced. The survival time after the first year was, however, only slightly better as compared with left bundle-branch block, (5.7 and 4.9 years respectively), possibly because of the greater mortality of the right bundle-branch block patients in the younger age group in which this was mostly associated with rheumatic heart disease.[11] If the series in which right bundle-branch block was associated with coronary heart disease were analyzed separately, as was done by Vazifdar and Levine[12] in 1952, the prognosis in right bundle-branch block was distinctly better than in left bundle-branch block. They found also that among 31 patients with bundle-branch block who were alive and well with no other sign of heart disease 5 to 21 years after the electrocardiographic diagnosis of bundle-branch block, 27 had right and only 4 left bundle-branch block. Most authors agree that bundle-branch block, whether left or right, has little prognostic significance, if not associated with clinical heart disease[13, 14, 15] and that the causative heart disease and particularly cardiac enlargement are the determining factors in prognosis. It is, however, established that the Wilson type of right bundle-branch block is the one which more often occurs as an isolated electrocardiographic abnormality. Series of normal population are more convincing in this respect than the pathologic series published from cardiac clinics.

Among 100 electrocardiograms with bundle-branch block in an insurable group collected by Rodstein, Gubner, Mills, Lovell and Ungerleider,[16] 77 had right and 23 left bundle-branch block, while among 83 uninsurable patients with cardiac conditions the proportion was 65 and 35 per cent respectively. This difference in the series as a whole is not relevant. But there was a much greater incidence of right bundle-branch block in the younger age group, almost all insurable; out of 30 persons below the age of forty, 27 had right bundle-branch block, while left bundle-branch block increased with advancing age. Difference in mortality between right and left bundle-branch block was not considerable, but the mortality of the insurable group was similar to that of the population as a whole. Unfortunately, no account was taken of the type of right bundle-branch block. Among 29 members of the United States Navy with bundle-branch block electrocardiograms and no associated heart disease, 18 has a wide S pattern right bundle-branch block, and this was the case in four out of six in whom the abnormality was known to have existed for 8 to 19 years. Langley, Red and Utz,[17] who published the series forming part of 100 cases of bundle-branch block among 6900 members of the navy, emphasized the favorable prognosis of the Wilson type of right bundle-branch block. Fisch[18] reported 11 cases of the same type in patients without any evidence of heart disease, whose electrocardiograms were taken mainly as routine studies. Seven out of these 11 were aged 19 to 35 years. Wolfram[19] collected 52 patients with bundle-branch block and without significant heart disease; of these 35 had right, 17 left bundle-branch block. Out of 35 with right sided block 26 had no evidence of organic heart disease.

In a series of 6132 cases comprising 4387 cardiac patients and 1745 normal subjects, Taimont, Carouso, Mèje and Lenègre[40] found the Wilson-type block in 0.74 per cent of the normal subjects, in 2.25 per cent of those with left-sided heart disease, in 2.14 per cent of those with right sided heart disease and in 0.9 per cent of those with both ventricles affected. Its incidence in coronary and arterosclerotic heart disease was 4 per cent. Lepeschkin[20] estimated that from the clinical point of view about 40 per cent of the patients with "wide S" type of right bundle-branch block were apparently normal, and 50 per cent had no cardiac enlargement. In those with cardiac lesions, coronary or hypertensive heart disease was found in 60 to 70 per cent, valvular heart disease in 8 to 10 per cent, congenital heart disease in 1 to 5 per cent and acute or chronic cor pulmonale in the remainder. In incomplete right bundle-branch block the incidence is different, according to Michaelides, Costeas, Vitsaxakis and Lekos[21]; valvular and congenital heart disease accounted for about 40 per cent, arteriosclerotic and hypertensive heart disease for 18 per cent, chronic cor pulmonale for 16 per cent, while

there was no heart disease in 23 per cent of their series or in 50 per cent of the series of Masini, Testoni and Farulla[22].

The absence of clinical heart disease in many patients with right bundle-branch block has been explained by the anatomic peculiarities of the right branch of the bundle. Compared with the left one, which fans out broadly soon after its emergence from the fibrous septum, the right branch has a long isolated course until it branches out to the free wall of the right ventricle. The superficial situation beneath the septal endocardium and its unique blood supply by the septal branches of the left coronary artery make it particularly vulnerable in right ventricular dilatation, localized septal myocarditis, chronic coronary artery disease and acute septal infarction. To explain the presence of right bundle-branch block in patients under the age of 40, Vazifdar and Levine[12] suggested that it might be the residue of some harmless intercurrent virus infection involving the myocardium, while Goldberger[23] even denied its pathologic significance and regarded it merely as a physiologic variation of conduction. The rare instances in which transient right bundle-branch block appeared under sympathetic overstimulation[24] or following startle reaction[25] give some support for this contention.

Faced with an electrocardiogram showing a Wilson type of right bundle-branch block, the physician may make one of the following interpretations: (1) that it represents only a functional variation of the conducting system; (2) that it has limited diagnostic significance, being the relic of an extinct process, myocardial or coronary, involving the right branch; (3) that it has diagnostic significance denoting an acute condition injuring the right branch, such as a circumscribed or extensive septal lesion; that it is due to right ventricular hypertrophy.

Evidently, the decision rests with the other findings, clinical, radiologic and electrocardiographic, showing the presence and extent of the cardiac affection. If the patient is under 40 and the heart otherwise normal, the electrocardiographic signs will carry little diagnostic or prognostic value. In patients over 50, in the same circumstances, some doubts may arise, particularly in connection with life insurance risks. If, on the other hand, a cardiac lesion coexists, the difficulties of interpretation will be considerable, particularly in patients with anginal pain where right bundle-branch block may be as much a sign of recent infarction as of a healed lesion.

In the hope of solving at least some of these problems we have investigated the diagnostic and prognostic significance of the changing electrocardiogram in the Wilson variety of right bundle-branch block.

Material

Fifty-three consecutive patients with records of Wilson (wide S) type of right bundle-branch block, in whom more than one record was available, were collected. The selection was based on the usual criteria of a QRS complex at least 0.11 second wide in which a slender R of normal voltage preceded a wide slurred S wave in lead I or II, and where a secondary R wave with a delay of at least 0.07 second was recorded in right ventricular leads. Our cases, therefore, belong to group II and III of Bayley's[26] classification; some difficulty was experienced in the selection of cases with cardiac infarction or right ventricular hypertrophy where R_1 may become lower than S_1 is deep. If there was doubt, the patient was included in the series, provided V_1 or V_2 confirmed the existence of right bundle-branch block. The cases fell into two main groups: group A comprising 33 patients with known episodes of cardiac infarction; group B comprising 20 patients in whom no infarction had taken place.

Group A included six patients with increasingly severe angina in whom it could be assumed on clinical grounds that infarction had occurred, though their records showed only right bundle-branch block. No previous normal records were available for comparison in four patients. Out of these 33, the electrocardiogram changed in 19. The changes were from normal QRS to persistent right bundle-branch block, from infarction pattern to transient or persistent right bundle-branch block or the reverse, and the various combinations of infarction patterns added to right bundle-branch block and

Table 1.—*Age and Sex in 53 Patients with Wilson Type of Right Bundle-Branch Block*

	11–19	40–49	50–59	60–69	70–79	Total
Males	1	6	10	13	15	45
Females	—	2	2	—	4	8
	1	8	12	13	19	53

Proportion of men to women = 6:1

their regression. Out of 20 patients in group B serial electrocardiographic changes were found in four. They included transient right bundle-branch block and the addition of A-V block to right bundle-branch block. More than half of the patients in the whole series were over 60 years of age. There were six times as many men as women (table 1).

Results

Group (A). Thirty-three Patients with Known Cardiac Infarction

Table 2 summarizes the findings in this series. Slight cardiac infarction, where cardiac pain is the only feature, and severe cardiac infarction where shock and failure dominate the picture, produce right bundle-branch block in equal proportion, and this is even more the case if the infarction is anterior. When right bundle-branch block is associated with posterior infarction the lesion is almost always severe. The six patients with increasingly severe angina, in whom there were no additional electrocardiographic changes, were listed as having had slight infarctions. The survival period was calculated to the end of the second month after infarction; no follow-up study is included.

In table 3 are listed the electrocardiographic serial changes in 19 patients of group A, those with infarction. Right bundle-branch block was an early manifestation of cardiac infarction in 15; in four of these it was intermittent with normal complexes or with left bundle-branch block (cases 3, 9, 14 and 5). It did not abolish the signs of anterior infarction and these regressed in most instances, leaving right bundle-branch block with flat or inverted T waves in some of the left ventricular leads. It was transient in three patients where normal QRS (cases 6, 14 and 16) with infarction pattern appeared temporarily or became the stable pattern. In case 13 it developed gradually through the pattern of partial right bundle-branch block. In Case 16 it regressed gradually, leaving a pattern of partial right bundle-branch block within 6 to 14 months of anterior infarction. In case 8 with septal infarction, right bundle-branch block appeared the day before death. In two (cases 7 and 18) with clinical infarction, the right bundle-branch block pattern did not change; in both of these, normal electrocardiograms were available for comparison. In case 18, the right bundle-branch block took many years to develop through the intermediate stage of partial right bundle-branch block. It was found one year before infarction, and remained unchanged for months after it. Two and a half years later the right bundle-branch block disappeared, leaving a record of left ventricular strain (fig. 1). The three patients in whom normal electrocardiograms were available before right bundle-branch block developed all showed S waves in lead I or II, whether the heart was horizontal or vertical. No right ventricular leads were available to decide whether this was already the expression of partial right bundle-branch block.[27] The addition of A-V block to right bundle-branch block was seen once in anteroseptal and twice in posterior infarction, all severe. The following examples illustrate our findings.

Table 2.—*Group A. Right Bundle-Branch Block with Cardiac Infarction in 33 Patients*

Severity	No. of cases	Site of infarction					Sev. ang.	Alive	Dead
		Ant. sep.	Ant. lat.	Post.	Ant. post.	Sep.			
Slight....	16	8	—	1	—	1	6	15	1
Moderate.	2	—	1	1	—	—	—	1	1
Severe...	15	6	1	6	1	1	—	8	7
	33	14	2	8	1	2	6	24	9

Severe Septal Infarction and Right Bundle-Branch Block. The first record shown in figure 2 was taken a few hours after infarction accompanied by loss of consciousness and profound shock which lasted until death three days later; it shows subendocardial ischemia in the lateral areas of the left ventricle (leads aV_L and V_6) with reciprocal changes in aV_R (acute septal ischemia) (fig. 2*A*, case 8). The second record taken two days later and one day before death, shows right bundle-branch block with anteroseptal infarction, best seen in V_2, V_3 and V_4, where notched and wide Q waves of 0.06 mm. precede the secondary R wave (fig. 2, *B*). The RS-T pattern in V_2 is the one repeatedly observed in other cases of right bundle-branch block with infarction; it consists of an RS-T period strictly level and isoelectric which passes abruptly into an inverted V-shaped ter-

TABLE 3.—*Serial Electrocardiographic Changes in Right Bundle Branch-Block with Infarction (19 Patients)*

Case No.	Age	Sex	Severity	Site	First ECG.	Interm. ECG.	Final ECG.	Result
Case 8. Fig. 2.	73	F	severe	sept.	subendo. isch.	—	R.B.B.B.; ant. lat.	died. P.M.
Case 4.	58	M	slight	ant.	ant. sept. R.B.B.B.	regression infarct pattern	R.B.B.B.	died 1½ yrs. later in attack
Case 1.	69	M	moderate	ant. sept.	ant. sept. R.B.B.B. A-V Bl.	regression infarct pattern	R.B.B.B. A-V Bl.	died 2½ yrs. later in C.H.F. P.M.
Case 2.	63	M	moderate	ant. lat.	ant. lat. R.B.B.B.	—	regressing infarct pattern	died 1 month later in attack.
Case 5.	67	M	severe	ant. sept.	ant. sept. R.B.B.B.	L.B.B.B.	L.B.B.B.	recov.
Case 10. Fig. 4.	70	M	slight	ant. sept.	ant. sept. R.B.B.B.	regressing infarct pattern	same	recov.
Case 12.	78	M	slight	ant.	ant. sept. R.B.B.B.	—	R.B.B.B. isch.	recov.
Case 13.	77	F	slight	ant. lat.	ant. QRS normal	regressing infarct pattern; part. R.B.B.B.	R.B.B.B.	recov.
Case 16. Fig. 5.	56	F	slight	ant. sept.	R.B.B.B.	normal QRS; ant. sept. later; R.B.B.B.	partial R.B.B.B.	well
Case 11.	77	M	slight	ant. lat.	altern. R.B.B.B. and normal QRS.	—	normal QRS; flat T1	recov.
Case 14.	42	M	severe	ant. lat.	interm. R.B.B.B. P-R + T_1 inv.	same	normal 4 yrs. later	well
Case 17.	54	M	slight	?	normal 1949.	R.B.B.B. 1951	same 1953	well
Case 18. Fig. 1.	62	M	slight	?	part. R.B.B.B. (1938)	R.B.B.B. (1946–1951); same after inf.	normal QRS. L.V. strain (1953)	cerebral thrombosis
Case 15. Fig. 10.	60	M	slight	post.	R.B.B.B.	post. inf. R.B.B.B.	R.B.B.B.	well
Case 9.	71	M	severe	post.	post. altern. R. & L.B.B.B.	post. R.B.B.B.	regressing infarct pattern	recov.
Case 3.	72	M	severe	post.	altern. R. & L.B.B.B. A-V B.	post. R.B.B.B.	same	died 1 month later
Case 7. Fig. 9.	77	M	severe	post. ant.	post. R.B.B.B.	R.B.B.B. & A-V B.; later flutter.	posteroant. & R.B.B.B.	well
Case 6. Fig. 8.	54	M	severe	post.	post. QRS normal. P-R norm.	R.B.B.B.; P-R 0.4 sec.	post.; QRS normal.; P-R 0.2	died 2 wks. later
Case 19. Fig. 7.	65	M	slight	ant. sep.	R.B.B.B. ant. sept.	—	R.B.B.B. only (3 wks. later)	recov.

C.H.F. = Congestive heart failure.

inal T. Thus, the usual signs of acute myocardial injury seem absent, for the RS-T period is not elevated or humped. The right bundle-branch block is here not of the Wilson type, for R_1 has a small voltage; but this is due to the acute injury to the left ventricle and the absence of opposing left ventricular potentials. (cf. the minute R in V_7). There is complete heart block. At necropsy (fig. 3) there was a recent infarct in the interventricular septum and the adjacent portion of the anterior and posterior wall of the left ventricle. The anterior part of the septum was thinner than the posterior part and the ventricle was here beginning to dilate. The right atrium and ventricle were dilated. The remainder of the myo-

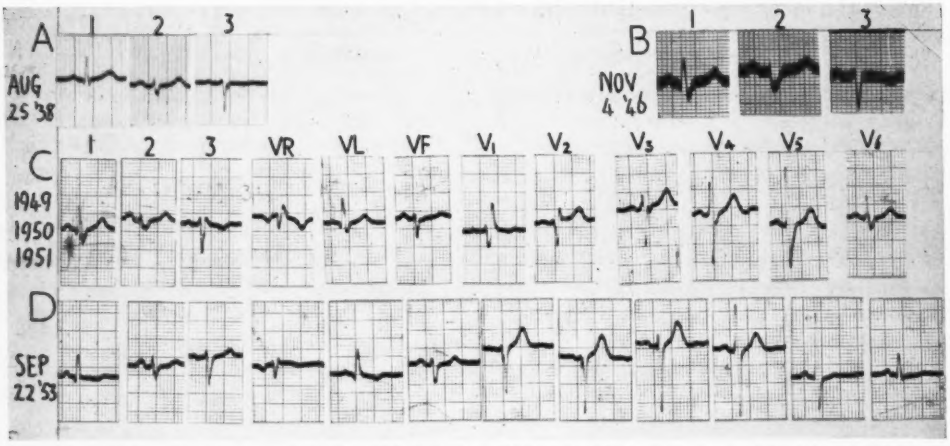

FIG. 1. Case 18. A man, age 61. Partial right bundle-branch block at the age of 39 (*A*). Complete Wilson-type block at the age of 47 when hypertension was found (*B*). Record unchanged during three years while clinical cardiac infarction occurred (*C*). Disappearance of Wilson-type block and pattern of left ventricular strain (*D*).

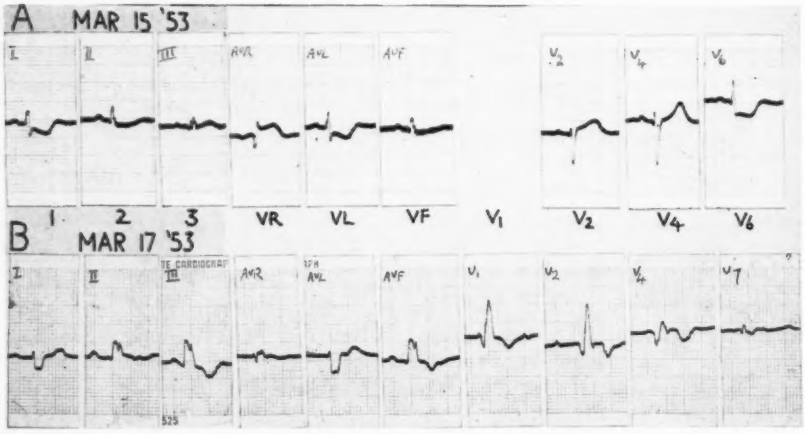

FIG. 2. Case 8. A woman, age 73. Subendocardial infarction (*A*), followed by Wilson-type block and anteroseptal infarction two days later, one day before death (*B*).

cardium showed diffuse patchy fibrosis. Severe calcified atheroma in both coronary arteries and their main branches considerably reduced the vascular lumen, but no occluding thrombus could be found.

Slight Anteroseptal Infarction and Right Bundle-Branch Block. The records of case 10, a patient with hypertensive heart disease, aortic incompetence and gradually worsening angina, portray the combination of right bundle-branch block, anteroseptal infarction and left ventricular hypertrophy (fig. 4). The Q waves in V_1 and V_2 may not be due to septal necrosis. The initial R is absent because the heart is enlarged and V_1 faces the right auricle (P in V_1 is inverted). The depth of Q is determined by left ventricular hypertrophy; in fact a minute R appears in V_2.[28, 41] The subepicardial infarction is here shown by the RS-T and T deformities in V_1, V_2, V_3 and V_4 and their successive regression. The first record again shows, in V and V_2, the abrupt terminal T inversion from

a horizontal RS-T level, which in successive records changes into the gradual R-T slope which imperceptibly fuses with an inverted T and so becomes the pattern of bundle-branch block and not that of an infarction.

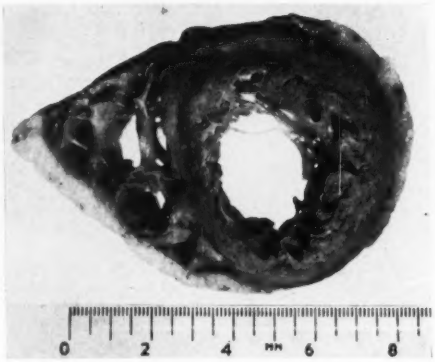

FIG. 3. Case 8. Postmortem specimen of patient shown in figure 2. Septal infarction with extension to anterior and posterior wall of the left ventricle is present.

Case 16 had a solitary bout of pain lasting half an hour without clinical or laboratory signs of infarction; this was followed during subsequent weeks by occasional attacks of angina. The electrocardiogram showed right bundle-branch block only (fig. 5*A*). One month later the record showed normal QRS with T inversion in V_1, V_2, V_3 and V_4, the pattern of anteroseptal subepicardial infarction (fig. 5*B*); successive records at one and three months showed a reversion to right bundle-branch block pattern, but T in V_4 became flat (fig. 5*C*). The record five months later showed restoration almost to normal except for V_1, where a secondary R wave, 0.08 second after the beginning of QRS, proved, that incomplete right bundle-branch block still existed (fig. 5*D*). One year after infarction the Wilson block reappeared with upright T waves in V_2 and V_3 (fig. 5*E*).*

* This patient had a recent anterior transmural infarction in the area of the previous subepicardial infarct, from which she recovered.

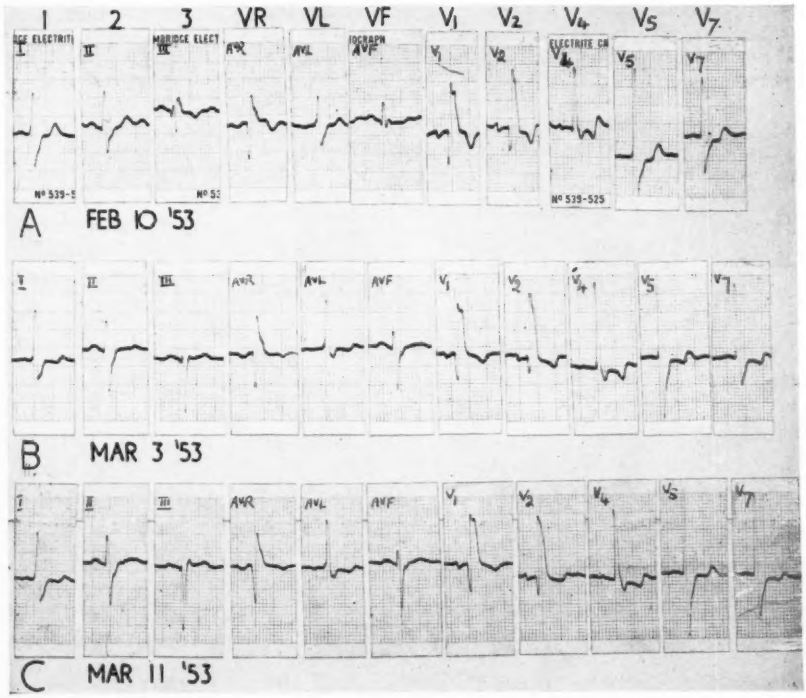

FIG. 4. Case 10. A man, age 70. Wilson-type block, left ventricular hypertrophy, anteroseptal infarction (*A*). Partial electrocardiographic recovery (*B*) and (*C*).

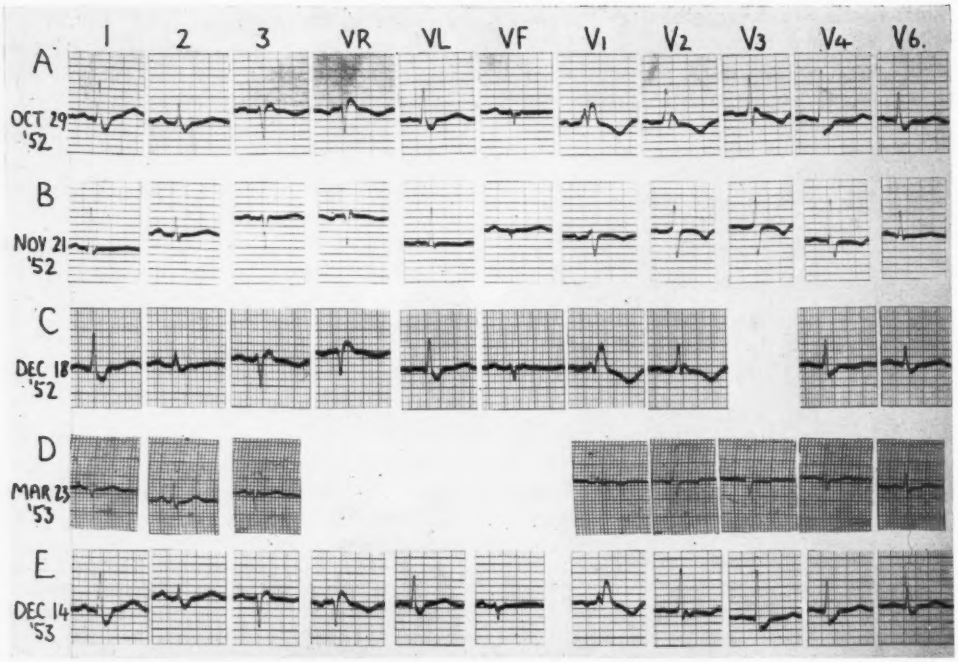

FIG. 5. Case 16. A woman, age 56. Wilson-type block following slight cardiac infarction (*A*) and (*C*), alternating with anteroseptal pattern (*B*). Regression of infarction pattern, partial right bundle-branch block remaining in V_1 (*D*). Wilson-type block with recovery of T waves in V_2 and V_3 one year after infarction (*E*).

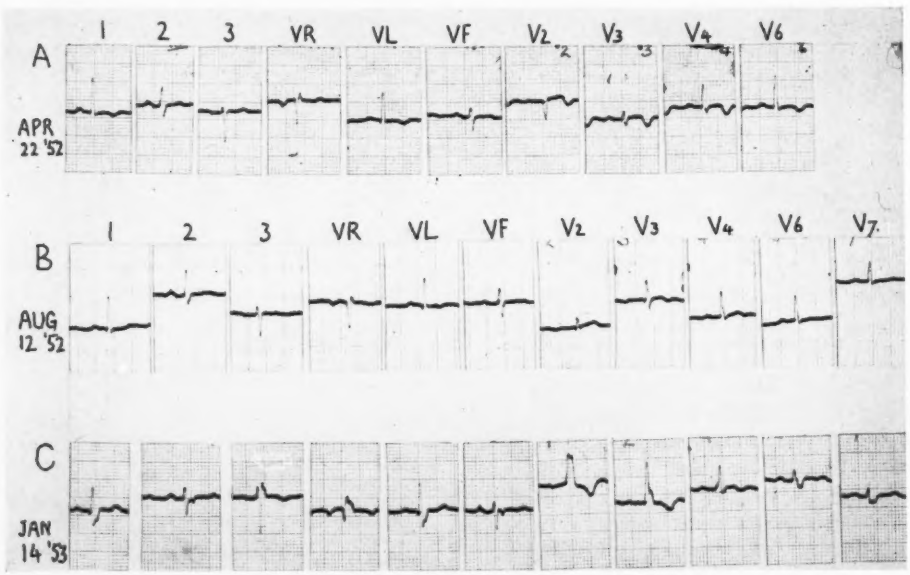

FIG. 6. Case 13. A woman, age 77. Anterolateral infarction (*A*) with electrocardiographic recovery (*B*). Wilson-type block nine months after infarction (*C*).

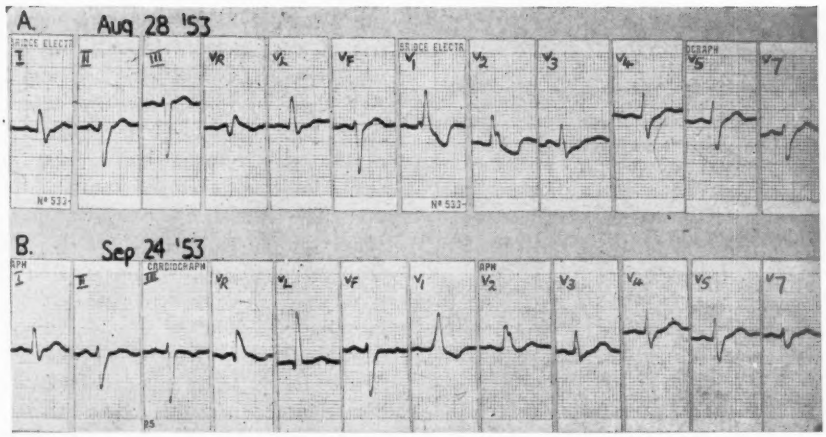

FIG. 7. Case 19. A man, age 65. Wilson-type block and anteroseptal infarction (*A*). Complete regression of infarction pattern one month later (*B*).

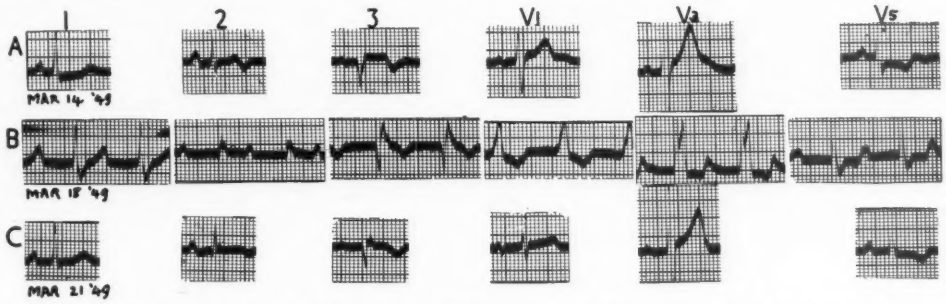

FIG. 8. Case 6. A man, age 54. Posterolateral infarction (*A*). Wilson-type block and latent heart block (P-R = 0.38 second) obliterating the signs of posterior infarction (*B*). Reappearance of infarction pattern with QRS of normal duration and P-R of 0.20 second (*C*).

The records of case 13 show this development in reverse. Here, too, cardiac infarction six weeks previously was followed by sporadic attacks of angina. The first record of figure 6 showed the pattern of extensive anterolateral, subepicardial injury from V_2 through V_6, with corresponding appearances in aV_L (fig. 6*A*). The next record revealed the regression of these signs, but with simultaneous development of incomplete right bundle-branch block in V_2 (fig. 6*B*). The third record, made nine months after the first showed complete right bundle-branch block which has remained the stable pattern since (fig. 6*C*).

While in figures 4 and 6 some ischemic relic remained months after infarction (flat or inverted T waves in left ventricular leads), the record of case 19 showed restoration to pure Wilson block pattern three weeks after slight anterior infarction (fig. 7*A* and *B*).

Severe Posterior Infarction and Right Bundle-Branch Block. Case 6 was admitted to a hospital with cardiac pain which had been persisting for more than two days. The first record in figure 8 showed posterior infarction (*A*); the second record (*B*) showed only right bundle-branch block with latent heart block; the deep Q_3 and the inversion of T_3 were in keeping with the Wilson block; the only sign significant of infarction was the RS-T depression in V_5. The Wilson type block did not reappear in subsequent records (*C*). The patient died 16 days after admission.

Some of the arrhythmias which may be associated with right bundle-branch block in severe posterior infarction are illustrated in fig-

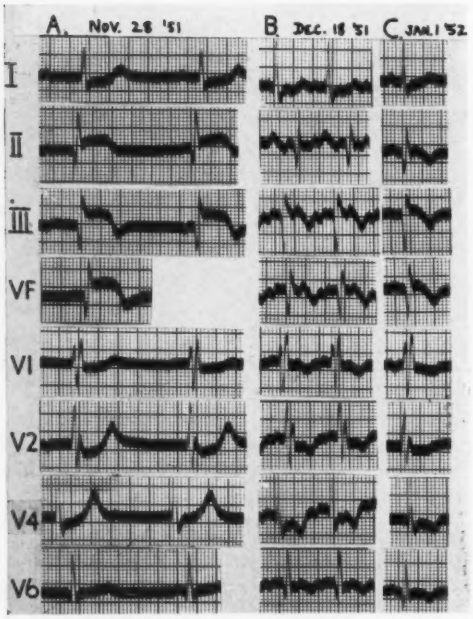

FIG. 9. Case 7. A man, age 70. Wilson-type block with complete A-V block in extensive posterior infarction (*A*). Wilson variety of block with 2:1 flutter (*B*). Sinus rhythm and pattern of posteroanterior infarction (V_2–V_6) denoting septal involvement (*C*).

ure 9 (case 7). The electrocardiogram on the day of admission in this critically ill patient, who eventually recovered, showed complete A-V block with acute posterior infarction and right bundle-branch block (fig. 9*A*). Sinus rhythm was restored the next day, but three weeks later he developed auricular flutter (fig. 9*B*). The record five weeks after admission again showed sinus rhythm; the infarct had then extended to the anterior wall by extensive septal involvement (posteroanterior infarction) (fig. 9*C*).

Slight Posterior Infarction and Right Bundle-Branch Block. There was only one solitary bout of moderate pain in this hypertensive and obese patient (case 15) who is considered under the heading and whose tracings are shown in figure 10. He had slight pyrexia for one day and no further attacks of chest pain followed. An electrocardiogram recorded three years previously showed an S_1 with horizontal heart; this suggests partial right bundle-branch block though no right ventricular leads were then recorded to confirm this (fig. 10*A*). The electrocardiogram a few hours after the attack showed a Wilson block, but nothing suggesting recent in-

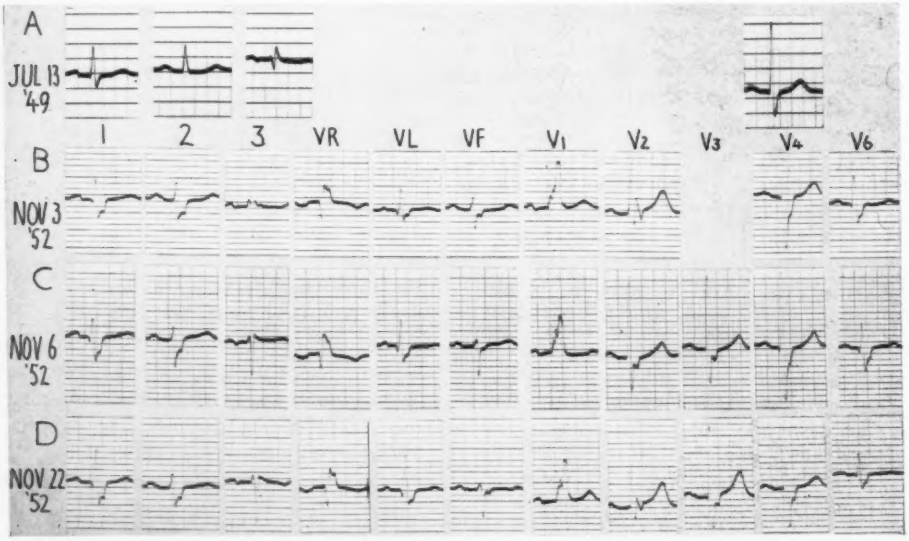

FIG. 10. Case 15. A man, age 60, with slight posterior infarction in association with pre-existing Wilson form of block. S wave in lead I with horizontal heart suggests incomplete right bundle-branch block in 1949, no right ventricular leads recorded (*A*). Wilson variety of block the day of clinical infarction; tall T in V_2 suggests posterior infarction (*B*). R-T elevation' in leads II, III and aV_F confirms posterior infarction (*C*). Regression of acute changes, flat T in V_6 (*D*).

TABLE 4.—*Right Bundle-Branch Block Without Cardiac Infarction in 20 Patients*

Diagnosis	No. of cases	Card. enl.	Cong. heart fail.	No. card. enl.	Aur. fibr. & flutter	A-V block.
A.S.H.D. & H.H.D.	9	7	5	2	2	3
M.S.	2	2	—	—	1	1
A.S.	1	1	—	—	—	1
A.S.D.	1	1	—	—	—	—
Chron. Cor pulm.	2	—	—	2	—	—
Lone aur. fibr. & flutter (parox)	3	—	—	3	3	—
No H.D.	2	—	—	2	—	—
	20	11	5	9	6	5

A.S.H.D. = arteriosclerotic heart disease; H.H.D. = hypertensive heart disease; M.S. = mitral stenosis; A.S. = aortic stenosis; H.D. = heart disease; A.S.D. = atrial septal defect.

and they were listed as having chronic cor pulmonale. Out of the remaining five, lone auricular fibrillation was present in two, and paroxysmal flutter in one, while two had no heart disease to account for the bundle-branch block.

The serial electrocardiographic changes in this group are summarized in table 5. In three out of four at one time or another, during their protracted illnesses, A-V block was recorded and two of them were in congestive heart failure. In case 35, who had fainting attacks suggesting the Stokes-Adams syndrome, no A-V block could be recorded, though it is known that normal A-V conduction may exist between attacks when Stokes-Adams seizures are associated with bundle-branch lesions.[29] The cardiogram of right bundle-branch block was frequently replaced by normal QRS patterns (fig. 11), the P-R interval remaining normal. In case 40, who had mitral stenosis with little cardiac enlargement and no failure, the transient right bundle-branch block was governed by the ventricular rate (fig. 12). The critical rate at which right bundle-branch block ap-

TABLE 5.—*Electrocardiographic Changes in Right Bundle-Branch Block without Infarction in Four Patients*

Case No.	Age	Sex	Diagnosis	Card. enl.	Electrocardiographic changes	
					From	To
Case 35. Fig. 11.	73	M	A.S.	L.V.++	R.B.B.B.; normal P-R	Normal QRS L.V. strain
Case 39.	62	M	H.H.D.	L.V.++ C.H.F.	Altern. R.B.B.B. & normal QRS 2:1 A-V H.B.	R.B.B.B. & C. A-V B.
Case 40. Fig. 12.	43	F	M.S.	sl. no C.H.F.	2:1 A-VH.B. normal QRS; v. rate 40	R.B.B.B. v. rate 66–90
Case 52.	77	F	A.S.H.D.	Gross C.H.F.	R. & L.B.B.B.; P-R 0.3 sec.	R.B.B.B., C. A-V B.

A.S. = aortic stenosis; H.H.D. = Hypertensive heart disease; M.S. = Mitral stenosis; A.S.H.D. = arteriosclerotic heart disease; L.V. = left ventricle; C.H.F. = Congestive heart failure; A-V H.B. = Atrioventricular heart block; C. A-V B. = Complete atrioventricular block.

farction (fig. 10*B*). On the third day of illness, a 1 mm. RS-T elevation was seen in leads II, III and aV_F (fig. 10*C*). The suspicion of posterior infarction was confirmed by the appearance of an increasing height of T waves in V_1, V_2 and V_3 in later records when the posterior signs were regressing (fig. 10*D*). In the last electrocardiogram T_1 and T_{aV_L} became flat.

Group B. Right Bundle-Branch Block without Infarction

The relevant findings in these 20 patients are contained in table 4. Arteriosclerotic and hypertensive heart disease was present in nine, and in these cardiac enlargement of various degree was an almost constant feature, with congestive heart failure in five. Three had valvular, and one congenital, heart disease; in two, right bundle-branch block was associated with chronic bronchitis and advanced emphysema,

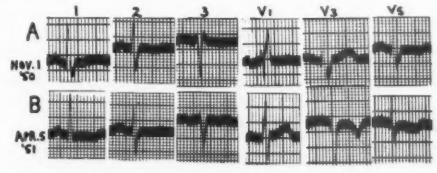

FIG. 11. Case 35. A man, age 73 with calcareous aortic stenosis. Transient Wilson block (*A*), alternating with QRS of normal duration and left ventricular strain pattern (*B*) at the same rate.

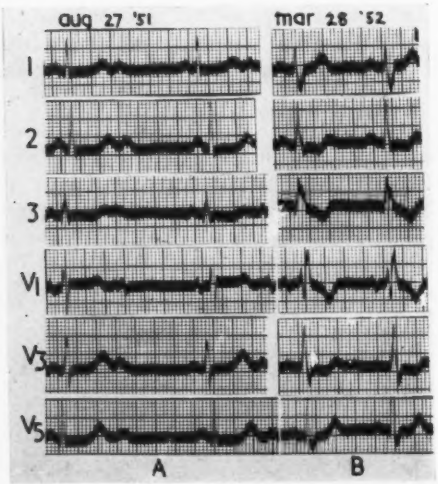

FIG. 12. Case 40. A woman, age 44, with mitral stenosis. A-V block (2:1) with normal QRS at a ventricular rate of 38 (*A*). Wilson form of block with normal A-V conduction at a rate of 68 (*B*).

peared was 66 to 90; when the ventricular rate fell to 40, through 2 to 1 A-V block, the ventricular complexes became normal.

DISCUSSION

The electrocardiographic signs of cardiac infarction associated with right bundle-branch block have been thoroughly investigated in recent years by Somerville and Wood,[30] and Dressler, Roesler and Schwager.[31] While left bundle-branch block obliterates the signs of infarction in more than half of the cases, in right bundle-branch block these signs could be identified in 93 per cent of the patients. The published cases, however, almost all belonged to the severe category where Q waves and RS-T elevation deformed the pre-existing right branch block pattern. How far right bundle-branch block may represent cardiac infarction when patterns representing such a lesion are not present in the cardiogram has remained unknown. The pathologic findings in most cases are also unhelpful, for they conform to the earlier conclusions of Master, Dack and Jaffe,[32] that there is no correlation between the vessels occluded or the location of the infarct and the type of conduction defect. Right bundle-branch block may even be associated with infarcts which do not reach the anatomic site of the right-bundle branch.[33] In the earlier histologic reports,[34, 36] the right bundle-branch block was only part of an extensive septal lesion which involved the left branch and the main bundle as well. It was only proved recently that an isolated interruption of the right branch of the bundle may be the only septal abnormality in Wilson block.[42] But still there is a contrast between pathologic studies which demonstrate a severe lesion in its final phases and the clinical observations which show the initial abnormality remaining unchanged for decades without the patient deteriorating.

The appearance of the Wilson type of right bundle-branch block as a transient phenomenon in "slight" anteroseptal infarction,[36] as in case 16, its gradual development following such a lesion as in case 13, and its sudden appearance without any additional signs of infarction in patients with anginal pain, as in case 17, shed light upon at least some of the cases. The right branch of the bundle is mainly supplied by the anterior perforating branches of the left coronary artery which is the artery more often affected. Since slight anteroseptal infarctions are not due to local arterial occlusions but to narrowing of the main coronary branch,[37] it is understandable how ischemia in this locality may involve this structure. The additional electrocardiographic signs of infarction, if present, are those of slight cardiac infarction though somewhat modified. Q waves in V_1 or V_2 may be present or absent, but T waves will always be inverted in most anterior chest leads; the RS-T elevation may not appear since the addition of the current of injury to the initial RS-T depression of the bundle-branch block pattern may result in an RS-T period strictly at a level and followed by a V-shaped terminal T inversion. As electrocardiographic recovery in these forms of infarction may be complete (case 19, fig. 7) or almost so (case 16, fig. 5), the right bundle-branch block may remain without the added signs of infarction, or with flat T waves in left lateral leads only, as in three instances in our series. Rodriguez and Sodi-Pallares[38] have shown that in dogs almost the whole of the thickness of the septum is activated by the left bundle branch. In right bundle-branch block

the delay in the activation of the right septal surface takes place in a relatively small area of 1.5 to 2 mm. thickness under the right septal endocardium in the lower third of the septum. In anteroseptal infarction, even if slight, this area may be easily damaged temporarily by edema, or permanently by scar formation, giving rise to right bundle-branch block, the presence of which does not make the prognosis any worse.

Right bundle-branch block was associated with slight posterior infarction only once in our series (case 16), and here it may have previously existed (fig. 10*A*). Its association with posterior infarction in five other cases, four of them with A-V block, alternating right and left bundle-branch block and posteroanterior infarction, proved that the extensive septal involvement reached the anterior third of the right septal area where the right bundle-branch is situated. Thus, the appearance of Wilson block in posterior infarction is a sign of increased severity. The signs of posterior infarction may be abolished by the coexistence of right bundle-branch block if the electrical axis is horizontal and a deep Q_3 is present; the addition of A-V block to right bundle-branch block in the presence of clinical signs of infarction (fig. 8*B*) is then a conclusive sign that extensive posterior infarction has taken place.

More than half of the patients in the group without cardiac infarction had enlarged hearts. Cardiac enlargement was slight in four and gross in six, and of these, five were in congestive heart failure. The electrocardiographic changes in these consisted in the appearance of A-V block or alternating right and left bundle-branch block in addition to the pre-existing Wilson block, and were thus similar to the changes found in severe anterior or posteroseptal infarction. The only difference was that these changes developed slowly and persisted for years; they were due to progressive septal fibrosis, which is part of the generalized myocardial sclerosis in these patients.

Transient right bundle-branch block (figs. 11 and 12) was seen in two patients with valvular heart disease. In the one with calcareous aortic stenosis there was gross cardiac enlargement and arteriosclerotic heart disease as well; in the other, a woman of 43 with mitral stenosis, cardiac enlargement was slight and there was no failure. Though the appearance of right bundle-branch block was here governed by the heart rate, in view of the existing rheumatic lesion the sympathetic influence must have been of secondary importance.

Sandberg, Wener, Master and Scherlis,[39] advocate right and left carotid pressure, exercise tests, inhalation of amyl nitrite and of 100 per cent oxygen for 20 minutes, various respiratory maneuvers and changes of posture to convert intermittent or transient bundle-branch block into normal intraventricular conduction or vice-versa. In their cases of right bundle-branch block their results were at least doubtful. Since transient and intermittent right bundle-branch block may be caused by just as serious heart disease as established right bundle-branch block, it is difficult to see the practical importance of carrying out these tests.

In nine patients the heart was found to be of normal size. Two were hypertensive and over 60 years of age; two had severe emphysema and chronic bronchitis. The diagnosis of right ventricular enlargement in its early stages is notoriously difficult, and we thought that right bundle-branch block might be the sign of this. They were listed as chronic cor pulmonale. Of the remaining five, two had lone auricular fibrillation, and one had paroxysmal flutter. There were only two patients in our series in whom Wilson block persisted as the only cardiac abnormality: a man, aged 62, in whom this was discovered 19 years previously, and a youth of 18. This is an incidence of less than 4 per cent. Admittedly, most of our patients were of arteriosclerotic age, but our material was not selected and comprised a consecutive series of patients seen in hospital, consulting and general practice. We therefore believe that the Wilson variety of right bundle-branch block without organic heart disease is rare. The myocardial condition which causes it may be slight or severe, extinct, quiescent or active. Its significance must be assessed on the basis of the clinical, radiologic and electrocardiographic findings. Studies of the serial changes in the electrocardiogram in 43 per cent of our patients provided us with information on the severity

and extent of myocardial damage and proved an important factor in assessment.

Summary

Out of a series of 53 consecutive patients with the Wilson variety of right bundle-branch block, 23 (43 per cent) showed serial changes in the electrocardiogram. These were investigated to establish their diagnostic and prognostic significance.

Clinical episodes of cardiac infarction occurred in 33, and electrocardiographic serial changes were found in 19 of these. These included changes from normal QRS to persistent right bundle-branch block, from infarction pattern to transient or persistent right bundle-branch block, or the reverse, and the various combinations of infarction pattern added to right bundle-branch block and their regression.

The Wilson variety of right bundle-branch block may be the only sign of slight anteroseptal infarction. This was proved in four patients where the added infarction signs regressed within weeks or months, leaving either a pure right bundle-branch block pattern or such added equivocal signs as flat T waves in one or more left ventricular leads. Conversely, in two cases, right bundle-branch block developed gradually within 6 to 14 months out of an anteroseptal infarction pattern. The involvement of the right bundle-branch in slight anteroseptal infarction can be explained by its anatomic proximity and by its unique blood supply from the left coronary artery. The addition of Wilson block to slight anteroseptal infarction does not make the prognosis worse.

In slight posterior infarction, the right branch of the bundle is hardly ever involved; in severe posterior infarction, right bundle-branch block suggests extensive septal involvement, which is proved by its frequent combination with A-V block, left bundle-branch block and posteroanterior infarction. Here it is of serious prognostic significance.

Anterior infarction may modify the pattern of the Wilson variety of right bundle-branch block; the diminution of left ventricular potentials may transform it into the classic pattern of right bundle-branch block. Conversely, right bundle-branch block may also modify the signs of anteroseptal infarction by obliterating the RS-T elevation of acute injury. Acute posterior infarction may not show in Wilson block with a horizontal heart; the additional A-V block with clinical signs of infarction is here diagnostic.

There was no evidence of infarction in the remaining 20 patients. The serial changes in four of these consisted in the additional appearance of A-V block and temporary reappearance of a QRS of normal duration. These changes were observed in patients with arteriosclerotic heart disease and cardiac enlargement which accounted for almost half of this group. In those without cardiac enlargement, right bundle-branch block remained a stable pattern; it was here associated with minor heart disease, such as chronic cor pulmonale, hypertension, auricular fibrillation or paroxysmal flutter. One patient in whom the appearance of transient right bundle-branch block was governed by the ventricular rate had mitral stenosis as well. Only in two instances was there no sign of additional heart disease, and this was less than 4 per cent of the whole series. We believe, therefore, that the Wilson type of right bundle-branch block is a sign of organic heart disease, although the latter may be so slight as to escape detection.

Summario in Interlingua

Le signification del bloco de branca dextere typo Wilson esseva investigate super le base de cambiamentos serial del electrocardiogrammas de quasi 50 pro cento de un serie consecutive de 53 casos de iste disordine. Le bloco de Wilson pote haber su origine in infarctos tanto anteroseptal como etiam posterior. In le infarctos anteroseptal illo pote representar un relicto sin importantia prognostic. In infarctos posterior illo indica un extense affection septal. Illo pote modificar le configuration lesional del infarcto anterior e supprimer le signos de infarctos posterior. Infarctos cardiac pote render lo simile al forma classic de bloco de branca dextere. Excepte in duo casos (i.e. in minus que 4 pro cento de serie), illo esseva invariabilemente connectite con causas pathologic Ergo on debe considerar lo como un signo de morbo cardiac organic.

ACKNOWLEDGMENT

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Studies on the Mechanism of Ventricular Activity

XIV. Clinical and Experimental Studies of Accelerated Auriculoventricular Conduction

By JEAN LOUIS BORDUAS, M.D., LOUIS RAKITA, M.D., REXFORD KENNAMER, M.D., AND MYRON PRINZMETAL, M.D.

Seven clinical cases with electrocardiographic patterns of constant or variable short P-R interval are reported. The QRS complex was either normal or aberrant. These abnormalities were reproduced experimentally in dogs by the injection of various drugs into the region of the A-V node. The theories advanced to explain these phenomena are discussed. The results indicate that accelerated A-V nodal conduction is responsible for the short P-R interval. The form of the ventricular complex may be dependent upon synchronous or asynchronous activity of the A-V node. A classification of A-V nodal dysfunction is presented.

PROLONGATION of the P-R interval was observed in the early days of electrocardiography, and the mode of occurrence has long since been established. The short P-R interval, however, was clinically recognized only recently[1] and there is still disagreement as to its underlying mechanism.

The major portion of the P-R interval has been demonstrated by Osborne and associates[2] to be a function of the A-V node; that is, the node normally delays the transmission of the impulse from auricle to ventricle. The most commonly recognized example of the short P-R interval is the Wolff-Parkinson-White (W-P-W) syndrome. In 1944, Öhnell[3] summarized the theories that had been presented to explain the short P-R interval seen in the Wolff-Parkinson-White syndrome. At present, the theories most commonly advanced are (1) the existence of a muscular or neuromuscular pathway, or pathways, between the auricle and the ventricle,[4, 5] (2) pre-excitation of a ventricular focus produced by electrical or mechanical stimulation from the auricles,[5, 6] and (3) acceleration of conduction time through the A-V node.[7]

We have recently observed cases in which the P-R interval was abnormally short, of constant or varying duration, and associated with normal or abnormal QRS complexes; the abnormal QRS complexes were narrow or wide. These cases are presumably not too uncommon, since six of the seven cases herein reported were observed in the ordinary course of private practice within a period of a few months. These cases are obviously not of the classic type of Wolff-Parkinson-White syndrome. Their clinical recognition and experimental reproduction constitute the subject of this paper.

CLINICAL DATA

Short P-R Interval, of Varying or Constant Duration, with Normal QRS Complexes

Case 1. D. P., a 16 year old boy, was seen for cardiac evaluation because of palpitation. The only positive findings disclosed by physical examination were a sinus arrhythmia and a grade I apical systolic murmur varying with respiration. Roentgenographically, the heart was well within normal limits.

The electrocardiograms (fig. 1*A* and *B*) revealed a sinus arrhythmia, with the rate ranging between 52 and 88 per minute. The P-R intervals varied

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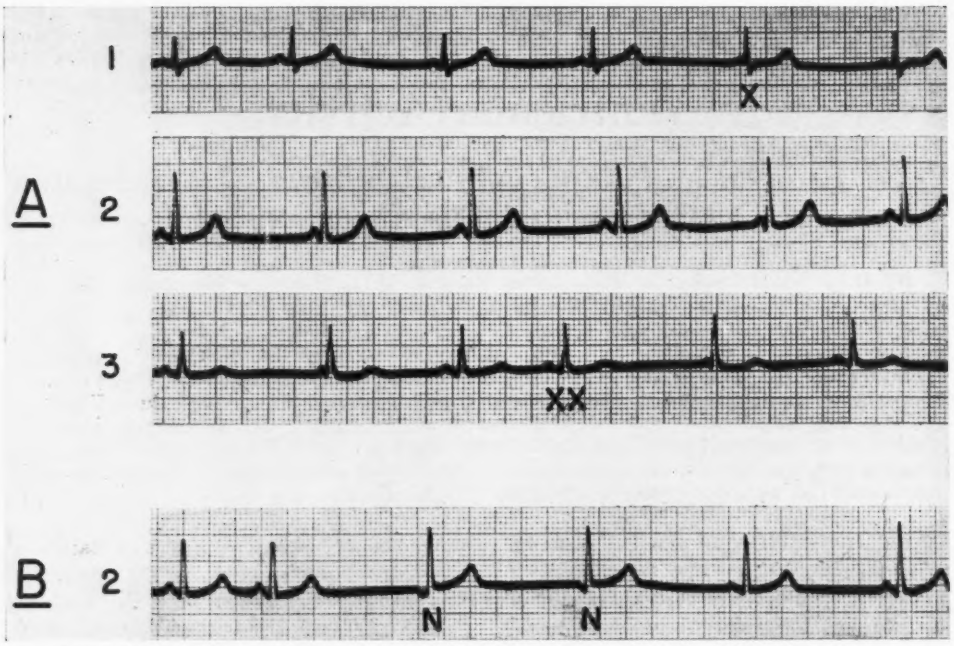


FIG. 1 (Case 1). Electrocardiograms of a 16 year old boy with no evidence of organic heart disease. (*A*) Leads I, II and III recorded at paper speed of 25 mm. per second. The P-R intervals vary from 0.06 (X) to 0.15 (XX) second. The QRS duration is within normal limits (0.06 second) and configuration is not altered by the short P-R intervals. Marked sinus arrhythmia. The rate varies between 52 and 88 per minute. (*B*) Lead II, after deep inspiration. The third and fourth complexes (N) are of upper nodal origin with retrograde auricular conduction. They are followed by resumption of the auricular pacemaker.

from 0.06 to 0.14 second. There was no relationship between P-R duration and R-R interval. The duration of the QRS was 0.07 second and configuration remained unchanged despite variations of the P-R interval. At the beginning of deep inspiration (fig. 1*B*) two A-V nodal beats with retrograde auricular conduction and inverted P waves were recorded in lead II, followed by resumption of the auricular pacemaker.

Case 2. W. T., a 49 year old white woman, was seen because of palpitation and backache. The past history, family history, functional inquiry and physical examination were noncontributory. Emotional instability, attributed to menopause, was noted.

Standard, unipolar and precordial leads (fig. 2) revealed a normal sinus rhythm (rate, 94 per minute) with P-R intervals unvaryingly of 0.11 second and QRS complexes of 0.04 second.

Case 3. J. P., a 56 year old white woman, was admitted to the hospital because of myocardial infarction. The patient had experienced chest pain on exertion, extending to the left arm and neck, for about 14 years. On the day of admission she had sudden onset of severe, persistent chest and neck pain, extending down the left arm, which necessitated admission to another hospital. Two weeks later she was transferred to this hospital. The only positive findings were an accentuated second aortic sound and a sedimentation rate of 28 mm. in 1 hour (normal, 0 to 20 mm.).

The electrocardiogram taken before myocardial infarction (fig. 3*A*) revealed normal sinus rhythm (rate, 75 per minute). The P-R interval was 0.16 second and the QRS complex 0.05 second. Shortly after infarction the electrocardiogram (fig. 3*B*) revealed sinus rhythm (rate, 68 per minute); the P-R interval varied from 0.12 to 0.04 second and the QRS was 0.06 second. Two weeks after myocardial infarction the electrocardiogram (fig. 3*C*) showed a normal sinus rhythm (rate, 75 per minute); the P-R interval was 0.14 second and the QRS 0.06 second.

*Case 4.** W. S., a 21 year old white soldier, was

* We are grateful to General Elbert DeCourse[illegible], Director of the Armed Forces Institute of Patholog[illegible], for permission to report this case.

admitted to Walter Reed Army Hospital from Camp Drum Army Hospital on June 28, 1952, with the complaint of difficulty in hearing since November 1950. Physical examination at Camp Drum had disclosed a cardiac arrhythmia. On admission to Walter Reed the patient stated that at the age of 17 he first experienced precordial aching associated with dyspnea, both of which followed exertion and disappeared with rest. On two occasions in 1950, associated with a severe "chest cold," he had hemoptysis of one cupful of bright red blood. At the time of physical examination the patient was in no apparent distress. The heart was not enlarged. The second pulmonic sound was split and louder than the second aortic sound. The blood pressure was 115/75. Results of the remainder of the physical examination were essentially normal. Laboratory tests, including urinalysis, serologic test for syphilis, blood count and sedimentation rate, were all within normal limits. Chest x-ray and fluoroscopy showed "minimal overlapping of the spine, in the left oblique, by the left ventricle, indicating slight enlargement of the ventricle." The heart size was increased 15 per cent over normal. The pulmonary artery shadow was prominent.

The numerous electrocardiograms (some of which are shown in fig. 4) were described as abnormal. Figure 4*A* reveals a sinus arrhythmia (rate, 97 to 110 per minute); the P-R interval is 0.20 second and the QRS 0.06 second. Figure 4*B* shows, in lead I, a sinus rhythm; the P-R interval varies from 0.06 to 0.21 second, and the QRS is of normal duration. In lead II, the second to seventh beats are nodal in origin and are associated with retrograde P waves and gradual lengthening of the R-P interval (reversed Wenkebach phenomenon). The initial beat in lead II shows a P-R interval of 0.12 second. The P-R interval following the return to sinus rhythm is 0.24 second. Lead aV_F is similar to lead II.

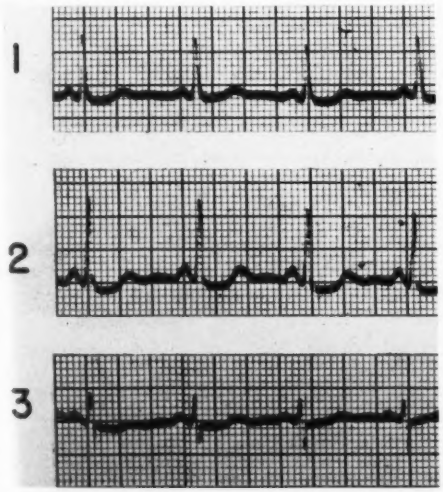


FIG. 2. (Case 2). Electrocardigrams of a 49 year old woman with no evidence of organic heart disease. Leads I, II, and III recorded at paper speed of 25 mm. per second. The P-R intervals are short (0.11 second) and of constant duration. The QRS is of normal duration (0.06 second) and configuration. Normal sinus rhythm; rate, 94 per minute.

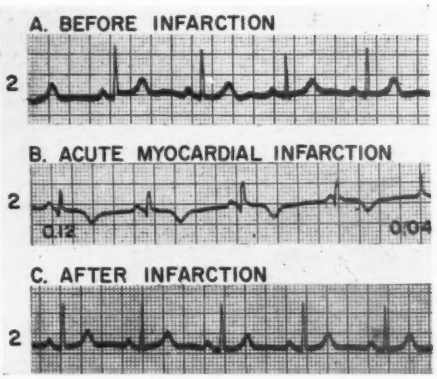


FIG. 3 (Case 3). Electrocardigrams of a 56 year old woman before, during and after posterior myocardial infarction. (*A*) Lead II, before myocardial infarction. The P-R interval is 0.16 second and the QRS duration 0.05 second. Normal sinus rhythm; rate, 75 per minute. (*B*) Six hours after myocardial infarction. The P-R interval varies from 0.12 to 0.04 second. QRS duration is 0.06 second. Sinus rhythm; rate, 68 per minute. (*C*) Two weeks after myocardial infarction. The P-R interval is 0.14 second. QRS duration is 0.06 second. Normal sinus rhythm; rate, 75 per minute.

While in the hospital, the patient suddenly died. Autopsy revealed hypertrophy of the right ventricular wall (7 mm.) and dilatation of the right ventricle immediately inferior to the pulmonary valve. The left ventricular wall measured 15 mm. in thickness. There were no valvular abnormalities. The pulmonary conus showed a minimal degree of dilatation. Microscopically the only finding in the myocardium was multiple small areas of infiltration from recent hemorrhage, with no associated inflammatory reaction. Examination of the lungs disclosed generalized atelectasis. There was extensive hyaline thickening of alveolar septal walls. Marked thickening of some of the arteriolar walls, principally intimal, was noted; in many instances the lumina of these arterioles were almost completely obliterated. The lesions were extremely patchy in distribution. The pathologist's diagnosis was "early primary pulmonary arteriosclerosis."

The foregoing cases illustrate that the P-R interval may be abnormally long (heart block) or abnormally short. The QRS complexes may be of normal duration and/or configuration.

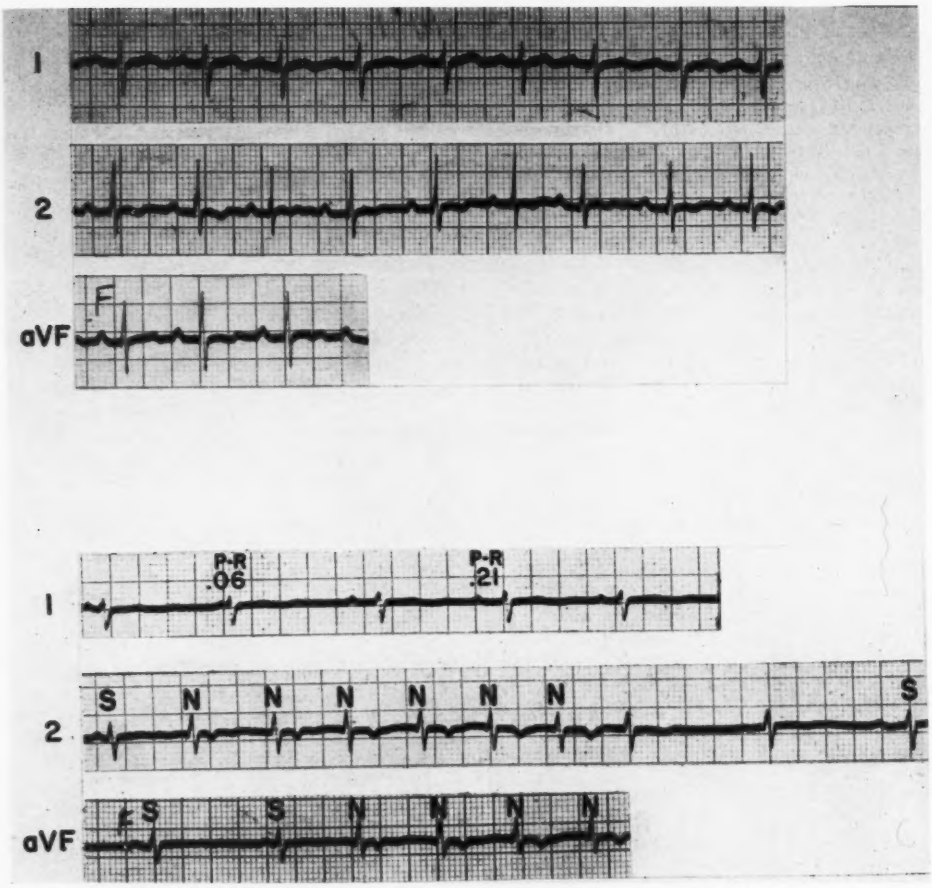


FIG. 4 (Case 4). Electrocardiograms of a 21 year old man with primary pulmonary arteriosclerosis. (*A*) Leads I, II and aV_F. The P-R interval is 0.20 second and QRS duration 0.06 second. Sinus arrhythmias, with the rate varying between 97 and 110 per minute. Paper speed 25 mm. per second. (*B*) Lead I. Sinus rhythm. The P-R interval varies from 0.06 to 0.21 second; the QRS is of normal duration (0.08 sec.). In lead II, the second to seventh beats (N) are of lower nodal origin, with gradual lengthening of the R-P interval (reversed Wenkebach phenomenon). The first sinus beat shows a P-R interval of 0.12 second. The P-R interval of the last complex is 0.24 second. In lead aV_F, the first and second beats are of sinus origin with P-R intervals of 0.14 and 0.10 second, respectively. The last four complexes are of nodal origin, with the same gradual R-P lengthening.

The duration of the short P-R interval may be variable (cases 1, 3 and 4) or constant (case 2). It is of interest that abnormally short P-R intervals may at other times be associated with partial heart block and A-V nodal rhythm in the same patient (case 4). The electrocardiographic deviations from normal in these cases may result from acquired disease (cases 3 and 4). Such deviations may also occur in the absence of any clinically demonstrable cardiac pathology as in cases 1 and 2. In these two instances there may have been a functional abnormality of the A-V node without structural changes.

Short P-R Interval, of Constant or Varying Duration, with Aberration of the QRS Complex

Case 5. R. C., a 22 year old white woman, was seen on Nov. 30, 1953, for cardiac examination. She

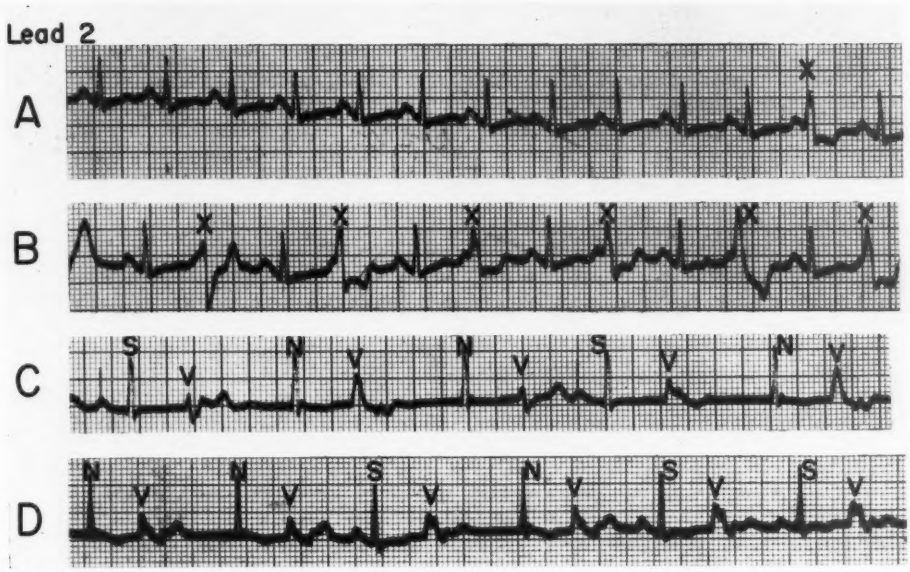


FIG. 5 (Case 5). Four electrocardiograms from 22 year old woman with no evidence of organic heart disease. Tracings recorded at intervals of several days. Paper speed 25 mm. per second. (*A*) Lead II. The P-R interval is 0.14 second, and QRS duration 0.06 second. At X the P-R interval is 0.10 second and the QRS is 0.11 second and of abnormal configuration. Sinus tachycardia; rate, 125 per minute. (*B*) Lead II. Alternating rhythm after exercise. Each normal complex is followed by a QRS complex of abnormal configuration. The P-R intervals of the normal beats are 0.14 to 0.16 second. QRS duration is 0.06 second. The P-R intervals of the abnormal complexes (X) vary from 0.08 second to unmeasurable. In the latter the initial upstroke of the QRS complex is due to the P wave. QRS complex follows P wave throughout entire tracing of which only a small portion is reproduced. (*C*) Lead II shows normal sinus complexes (S) with P-R intervals of 0.21 second, nodal complexes (N) and alternating ventricular extrasystoles (V). The ventricular extrasystoles are followed by upright P waves. (*D*) Lead II shows normal sinus complexes with P-R intervals of 0.16 second, nodal complexes (N) and alternating ventricular extrasystoles (V).

stated that several years previously, when she was being investigated for a gynecologic disorder, she was told that she had "heart disease." Since then she had had occasional episodes of palpitation. The past history, family history and functional inquiry were noncontributory. Chest x-ray and routine laboratory tests were all within normal limits.

The electrocardiogram shown in figure 5*A*, recorded two minutes after exercise, shows sinus tachycardia (rate, 125 per minute). The P-R interval is 0.14 second and the duration of the QRS complex 0.06 second. At X there is a single beat in which the P-R interval is 0.10 second and the QRS is 0.11 second and of abnormal configuration.

In figure 5*B*, recorded shortly after the electrocardiogram reproduced in figure 5*A*, lead II shows an alternating rhythm; each normal complex is followed by a QRS of abnormal configuration. The P-R intervals of the normal beats vary from 0.14 to 0.16 second and the QRS measures 0.06 second. In the abnormal complexes (X) the P-R interval is sometimes not measurable, because the P wave blends with the upstroke of the QRS complex. When measurable, the interval varies from 0.06 to 0.10 second, and the QRS complexes are obviously wider.

The tracings shown in figure 5*C* and *D* (lead II) exhibit normal sinus complexes (S), A-V nodal complexes (N) and alternating, premature ventricular complexes (V). Conducted auricular beats show a P-R interval of 0.21 second. Many of the premature complexes are followed by an upright P wave.

Case 6. R. H., a 50 year old white man, was admitted to the hospital because of sudden onset of severe, oppressive, substernal pain, associated with profuse sweating and profound weakness, which began one hour prior to admission. The blood pressure was 170/120, and there were moist rales at both lung bases posteriorly. The results of the remainder of the physical examination were negative. Urinalysis showed a specific gravity of 1.022, 3 plus acetone and 3 plus albumin; there were 1 to 2 white

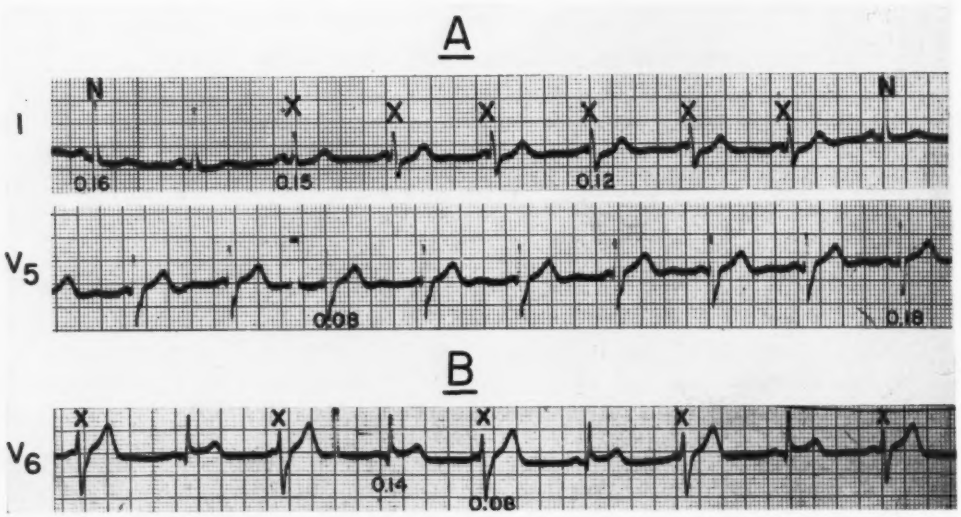


FIG. 6 (Case 6). Electrocardiograms of a 50 year old man following acute myocardial infarction. (*A*) Leads I and V_5 at paper speed of 28 mm. per second. The P-R intervals vary from 0.08 to 0.18 second. The short P-R intervals are associated with aberrant QRS complexes (X) of 0.08 to 0.12 second in duration. Sinus rhythm; rate, 68 per minute. (*B*) Lead V_6. Alternating rhythm. The P-R intervals of aberrant complexes (X) are of varying duration, 0.07 to 0.13 second. The P-R interval of most beats is 0.14 second.

blood cells, 1 to 2 hyaline casts and a few red blood cells per high power field. The blood count showed 20,100 white cells, with a differential count of 90 per cent polymorphonuclear leukocytes, 5 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate was 13 mm. in 1 hour (normal 0 to 9 mm.), and the fasting blood sugar level was 140 mg. per 100 cc. A diagnosis of acute myocardial infarction was made.

The electrocardiograms, of which two leads are illustrated (fig. 6*A*), reveal shortening of, and variation in, the P-R interval, associated with aberration of the QRS complex. The rate is 68 per minute; the P-R interval is 0.08 to 0.18 second, and the QRS is 0.06 to 0.12 second. Figure 6*B* reveals an alternating rhythm with short P-R intervals of varying duration, and aberrant QRS complexes of the alternate beats. The normal P-R interval is 0.16 second and QRS duration is 0.06 second. The P-R interval of the aberrant complexes varies from 0.07 to 0.13 second, and the QRS is 0.12 second. This rhythm reverted to normal after a short period of time and remained normal.

Several months later, while in another city, the patient had another episode of coronary occlusion, which resulted in his death. We were fortunate in being able to obtain the heart for histologic examination, which was done by the Lev technic.[5] The pathologist* reported that, in the node, "the amount of connective tissue and fat tissue would be considered about the upper limit of normal for a person 40 to 50 years of age."

Case 7. W. M., a 45 year old white man, experienced sudden onset of severe substernal pain, as-

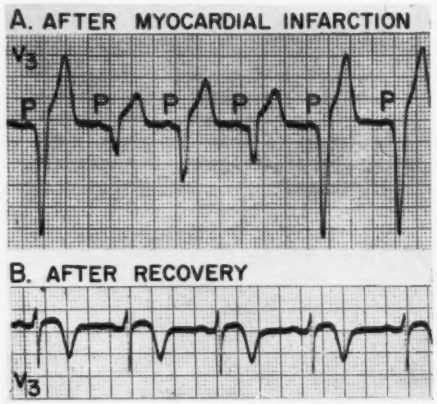


FIG. 7. (Case 7). Electrocardiograms of a 45 year old man following myocardial infarction. (*A*) Lead V_3, after myocardial infarction. There are short P-R intervals of varying duration (0.09 to 0.16 second). The QRS complexes are aberrant and of varying duration (0.08 to 0.12 second). Paper speed 22 mm. per second. (B) After recovery; the P-R intervals and QRS complexes have reverted to normal.

* The slides were examined by Dr. Harry Goldblatt, to whom we express our thanks.

sociated with profuse sweating and weakness. The pain was relieved by administration of 200 mg. of Demerol, and he was admitted to the hospital. Physical examination revealed tachycardia (rate, 160 per minute) and numerous ventricular extrasystoles. The blood pressure was 110/80. There were no other abnormalities noted on physical examination. Routine laboratory tests were within normal limits.

The electrocardiograms (fig. 7*A*) reveal short P-R intervals of varying duration (0.09 to 0.16 second), associated with wide and aberrant QRS complexes (0.12 second). In the electrocardiogram taken after recovery (fig. 7*B*) the P-R interval and QRS complex have reverted to normal (P-R, 0.16 to 0.20 second and QRS, 0.08 second).

The cases in this group illustrate that a short P-R interval may be associated with aberrant QRS complexes. In case 5 there were short P-R intervals of varying duration with normal and aberrant QRS complexes, nodal beats and ventricular extrasystoles, without any other clinical evidence of myocardial disease. At other times this patient manifested evidence of partial heart block with prolongation of the P-R interval. In cases 6 and 7, short P-R intervals with aberrant QRS complexes were noted in association with myocardial infarction. These three cases illustrate that the phenomenon may be associated with acquired cardiac disease (cases 6 and 7) or may exist in the absence of any clinically demonstrable heart disease (case 5).

The short P-R intervals with normal or abnormal QRS complexes observed in the clinical cases reported herein were produced in dogs by experimental alteration of the A-V node. Nodal rhythms and heart block, which occurred in some of the patients, were also produced by altering the A-V node in dogs. It is suggested, therefore, that the phenomena found in these patients may result from A-V nodal disturbances.

Experimental Study

Materials and Methods

Experiments were carried out in 40 dogs. Each animal was anesthetized with Pentothal or Nembutal administered intravenously. The animal was placed in a supine position and a control electrocardiogram taken. Tracheotomy was then performed. In some experiments the chest was opened through a right lateral incision in the third or fourth intercostal space. A bilateral incision was employed in other

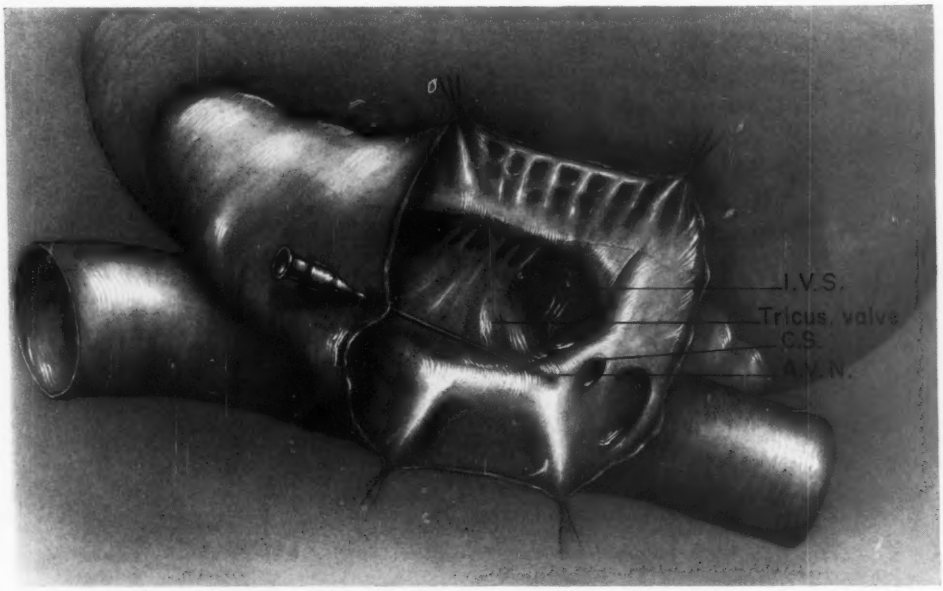


Fig. 8. Illustration of technic of injection into the A-V node through the body of the right auricle. For orientation the needle is advanced through the tricuspid valve until contact is made with the interventricular septum (I.V.S.). It is then withdrawn into the auricular cavity and directed caudally toward the coronary sinus (C.S.) until contact is made with the A-V node (A.V.N.).

experiments. After the chest was opened and the anterior pericardium removed, a second control electrocardiogram was made.

All tracings were made on a direct-writing Sanborn Poly-Viso electrocardiograph. Continuous recordings were made throughout each experiment, usually at a paper speed of 50 mm. per second. In addition, recordings were made on the Sanborn Twin Beam electrocardiograph, which has a frequency response of 500 cycles per second. The results were the same as with the Poly-Viso electrocardiograph.

In the earlier experiments, lead II was recorded simultaneously with aV_R or a direct auricular lead. Four simultaneous leads were recorded during the later experiments, usually including leads I, II, III and aV_R or a direct auricular lead. In several instances lead II and a direct auricular lead were registered simultaneously with direct right and left ventricular leads. The direct auricular leads were recorded with a cotton-tipped electrode sutured to the posterior auricular wall in the region of the coronary sinus.

The experimental procedure consisted of injecting the region of the A-V node with cocaine, formaldehyde or acetylstrophanthidin. These were chosen for the purpose of anesthetizing, destroying or depressing A-V nodal tissue. Two technics of injection were used:

1. A 22 or 23 gage needle, attached to a tuberculin syringe, was inserted through the hind portion of the right auricle and advanced through the tricuspid valve to the right side of the interventricular septum. The needle was then withdrawn into the auricular cavity and directed caudally and posteriorly until the A-V node was located (fig. 8).

2. The needle was inserted into the cavity of the right auricle through a purse string opening in the right auricular appendage. Then, by directing the needle cephalad from the coronary sinus, the A-V node could be reached.

Contact with the node was manifested by the occurrence of transient heart block of first, second or third degree, or nodal arrhythmias of short duration. After the position of the needle had been verified by these electrocardiographic changes, approximately 0.25 to 0.50 cc. of drug was injected into the A-V node. Upon completion of each of the experiments, the animal was sacrificed and the heart opened in order to verify further the site of injection. In al

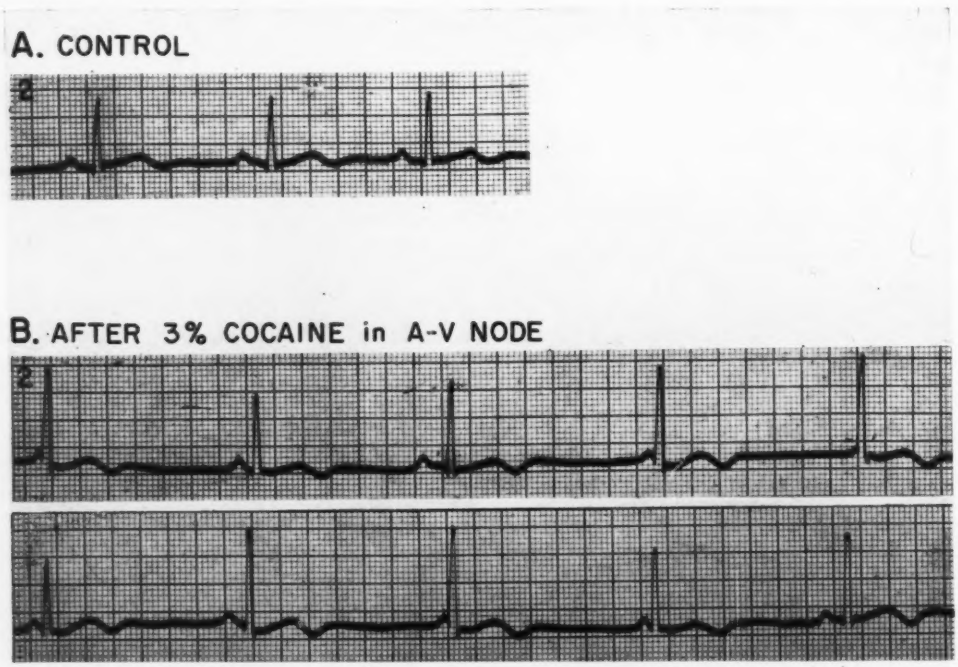


FIG. 9. Effect of injection of cocaine in the A-V node of a dog. (*A*) Control. Sinus rhythm; rate, between 96 and 106 per minute. The P-R interval is 0.12 second and the QRS 0.03 second. Paper speed, 50 mm. per second. (*B*) Continuous strip. Lead II. After injection of 3 per cent cocaine in the region of the A-V node. There is gradual lengthening, shortening and then lengthening of the P-R interval. The rate is 84 per minute. The P-R interval ranges from 0.04 to 0.13 second and the QRS is 0.04 second. Paper speed, 50 mm. per second.

experiments reported, a grossly edematous and hemorrhagic area approximately 5 mm. square was visible in the immediate vicinity of the A-V node between the coronary sinus and the posterior cusp of the tricuspid valve. Sections from five hearts were examined by the pathologist, using Lev's technic. These microscopic examinations confirmed the gross observation that the chemicals had been injected into the A-V node.

Thirteen of the 40 dogs received 20 per cent, 5 per cent or 3 per cent cocaine hydrochloride. In 7 of the 13, 20 per cent formaldehyde was injected after the effects of cocaine had disappeared. Twenty-one dogs were given 20 per cent formaldehyde alone. In the remaining six animals, 0.33 to 1.0 cc. (1 to 3 cat units) of acetylstrophanthidin was injected into the A-V node. Ten of the animals were used as controls; cocaine, formaldehyde or acetylstrophanthidin, in concentration similar to that injected into the A-V node, was injected peripherally into the free wall of the ventricles and into various parts of the interventricular septum.

Results

Control electrocardiograms with the chest closed or open were essentially normal, except that inversion of the T wave followed opening of the chest. After injection of cocaine or formaldehyde into the A-V node, variable shortening of the P-R interval was frequently observed. The P waves in standard limb leads were usually identical with, or only slightly different from those in the control electrocardiograms. The shortening of the P-R interval was correlated with changes in the P-R segment rather than with changes in duration of the P waves.

The results obtained in only 11 of the dogs are reported; the remaining animals developed heart block, nodal rhythms or nodal arrhythmias, or the short P-R intervals were not persistent for a long enough period of time to be considered significant. In the group reported, the pattern of varying short P-R intervals appeared within several seconds to very few minutes after the injection into the node and persisted from one to several minutes. After normal sinus rhythm recurred, the short P-R intervals could often be reproduced by a second injection.

Cocaine. The seven dogs that received injections of cocaine into the A-V node presented short P-R intervals of varying duration with QRS complexes of normal duration. In two of these animals (fig. 9*A* and *B*) gradual shortening, lengthening and then shortening of the P-R interval occurred within a period of several beats. There is a definite similarity between the pattern occurring in this animal and that in case 1 (fig. 1). The remaining five dogs presented short P-R interval variations with no apparent pattern. Although the duration of the P-R interval usually changed with each cardiac cycle, occasionally it remained constant for a few beats (fig. 10*A* and *B*). In three of the seven animals, the QRS complex was normal in configuration as well as in duration. In four animals the shape and amplitude of the QRS were altered (fig. 10*A* and *B*), but the duration remained within normal limits.

In two animals, 2:1 heart block followed the injection of cocaine into the A-V node. In one of these the QRS was of normal duration and

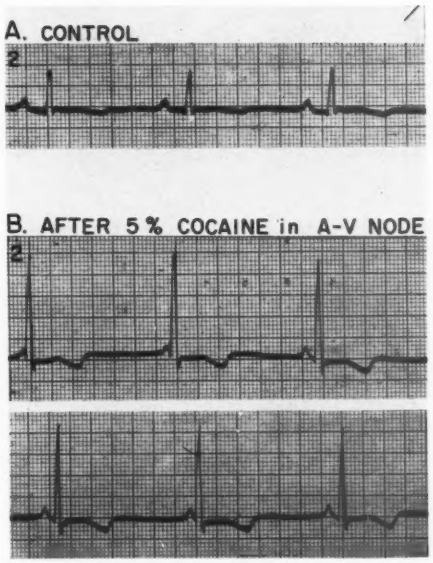


FIG. 10. Effect of injection of cocaine in the A-V node of a dog. (*A*) Control. Lead II. The rate is 90 per minute. The P-R interval is 0.12 second and the QRS 0.05 second. Paper speed, 50 mm. per second. (*B*) Continuous strip following injection of 5 per cent cocaine in the region of the A-V node. The rate is 86 per minute. The P-R intervals are 0.07 second. There is a marked increase in the amplitude of the QRS, although the duration remains approximately the same as in the control. Paper speed, 50 mm. per second.

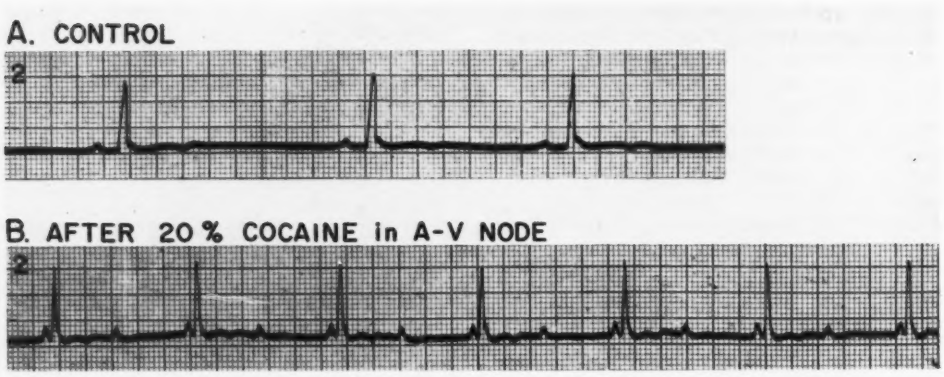


FIG. 11. Effect of cocaine in the A-V node of a dog. (*A*) Control. Lead II. The rate ranges between 64 and 80 per minute. The P-R interval is 0.12 second and the QRS 0.06 second. Paper speed, 50 mm. per second. (*B*) Lead II, after injection of 20 per cent cocaine in the region of the A-V node. There is a 2:1 heart block. The auricular rate is 110 per minute and the ventricular rate 55. The P-R intervals of the conducted beats are 0.04 second. QRS configuration is unchanged from the control and the duration is 0.08 second. Paper speed, 25 mm. per second.

configuration, while in the other the QRS was aberrant. The P-R interval of the conducted beat was extremely short in both animals (figs. 11 and 12).

Another point in figure 12 is noteworthy. By examining only lead II, one might diagnose the abnormality as first degree heart block with extremely long P-R intervals. It is only by examining the auricular lead that one observes a P wave immediately preceding the ventricular complex. The P wave is responsible for the initial portion of the R wave in lead II. Because the P-R interval is so short, the auricular and ventricular complexes in this lead appear fused. An important way of determining that the aberrant ventricular beat is preceded by a P wave is by accurate measurement of the P-P interval. It will then be found that the ventricular complex starts with a P wave.

Formaldehyde. Among the three animals that received formaldehyde injections and exhibited short P-R intervals, the shape of the QRS complex was normal in one and altered in two. Although the P wave in standard limb leads always remained upright, it was lower than normal in two dogs and higher than normal in one. In two dogs the P-R interval was short and varying in duration and was associated with an aberrant QRS complex (fig. 13); note the similarity to case 6 (fig. 6*A*, lead V_5).

Acetylstrophanthidin. One of the animals that received acetylstrophanthidin presented a very short P-R interval of unvarying duration,

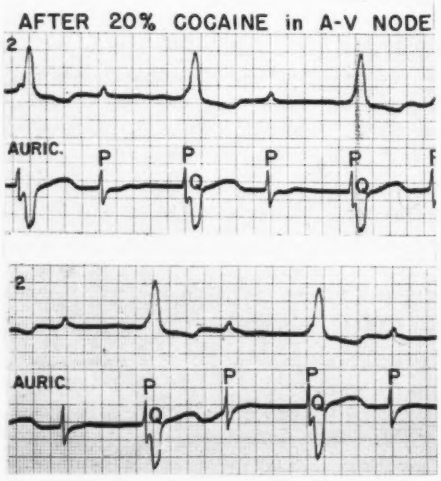


FIG. 12. Continuous strip of simultaneously recorded lead II and direct auricular lead after injection of 20 per cent cocaine in the region of the A-V node of a dog. There is 2:1 heart block. The auricular rate is 124 and the ventricular rate 62 per minute. In lead II the P waves preceding the QRS complex are not readily recognized. By inspection of the direct auricular lead, however, it is apparent that there is a P wave preceding the QRS complex and that the P-R interval is extremely short. The QRS complexes are markedly widened and aberrant. Paper speed, 50 mm. per second.

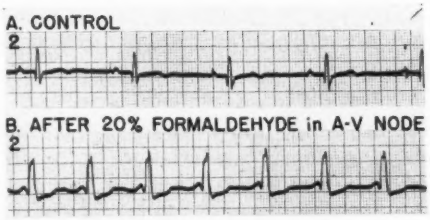


FIG. 13. Effect of formaldehyde in the A-V node of a dog. (*A*) Control. Lead II. The rate is 94 per minute. The P-R intervals are 0.10 to 0.12 second and the QRS is 0.06 second. Paper speed, 50 mm. per second. (*B*) Lead II, following injection of 20 per cent formaldehyde. The rate is 154 per minute. The P-R intervals are 0.05 to 0.07 second. The QRS complex is markedly aberrant. Paper speed, 50 mm. per second.

associated with a QRS complex of normal duration and configuration (fig. 14). The tracings are similar to those in case 2 (fig. 2).

Control Injections. The 10 control animals that received injections at sites other than the A-V node failed to show the above-described phenomena.

Conversion of Complete Heart Block to Short P-R Interval. Complete heart block was frequently observed after all three procedures. In some cases, after a short period of time, as the concentration of the drug in the node decreased, the complete heart block was

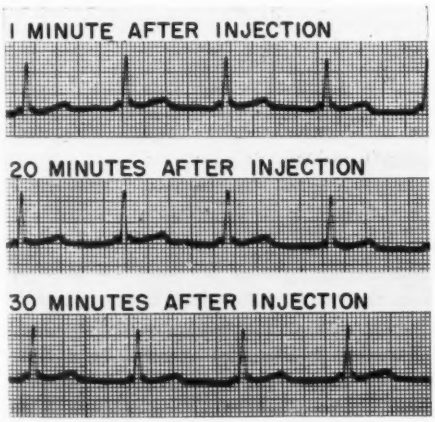


FIG. 14. Lead II following injection of acetylstrophanthidin in the A-V node of a dog. Three tracings from multiple recordings made over a 30-minute period following injection, illustrating persistence of the short P-R interval. The rate is 130 per minute. The P-R interval is 0.04 second and the QRS is also 0.04 second. Paper speed, 50 mm. per second.

followed by second and first degree heart block. As the heart block became less severe it was frequently associated with isolated beats, runs of beats or alternating complexes manifesting short P-R intervals, of constant or varying duration, and associated with either normal or aberrant QRS complexes.

DISCUSSION

In our experiments, alteration of the A-V node resulted in three phenomena: (1) heart block, (2) short P-R intervals and (3) nodal rhythms and arrhythmias. The short P-R interval was of constant or of varying duration, associated with normal or abnormal QRS complexes. These phenomena are comparable to those seen in the clinical cases. The pattern of constant short P-R interval was experimentally reproduced in one dog by injection of acetylstrophanthidin in the region of the A-V node. The varying type followed injections of cocaine or formaldehyde into the same region. These results are consistent with the clinical observation that short P-R intervals are frequently associated with acute myocardial disease involving the A-V node, such as acute rheumatic myocarditis and acute posterior myocardial infarction. Three cases have been reported[7a] in which acquired and permanent Wolff-Parkinson-White syndrome was associated with histopathologic changes in the region of the A-V node. Since there was no obvious cardiac pathology in some of our cases (cases 1, 2 and 5), it would appear that a dysfunction of the A-V node could be responsible for the electrocardiographic phenomena even in the absence of a definite lesion of this structure. In the one case in this series in which autopsy was done, the alterations in the A-V node were considered to be at the upper limit of normal. However, the autopsy was performed several months after the episode that was manifested by short P-R intervals in the electrocardiogram. It is probable that more significant pathologic changes might have been present during the acute episode.

Causes of Short P-R Interval

Various theories have been proposed to account for the occurrence of a short P-R in-

terval (0.12 second or less) in the clinical electrocardiogram. These theories will be discussed in relation to the results reported in this paper.

Autonomic Influences. In the first report of an electrocardiogram showing a short P-R interval associated with an abnormal QRS complex,[9] the phenomenon was considered to be due to vagal influence. This explanation was also advanced by Wolff, Parkinson and White, in their original article.[1] Since then there have been published many reports of the occurrence of short P-R intervals with normal QRS complexes in a variety of clinical syndromes: hyperthyroidism,[10] hypertension,[11] acute coronary thrombosis,[12] the neurotic state[13, 14] and associated with paroxysmal tachycardia.[15] The variation of the vagosympathetic tone was considered responsible for the shorter auriculoventricular conduction time.

It is well known that hypothalamic or drug-induced sympathetic stimulation results in sinus tachycardia and relative shortening of the P-R interval. In our clinical experience, however, when there is variation of what is referred to as "vagosympathetic tone," the P-R interval generally remains longer than 0.12 second. None of the drugs used in our experimental procedures has a known sympathomimetic effect; the effect of digitalis is mainly vagotonic. There was no indication in our experiments that the autonomic nervous system factor was responsible for the shortening of the P-R interval.

Ectopic Auricular Focus. Some workers have attributed the short P-R interval with a QRS complex of normal duration to the presence of a low ectopic auricular focus. Various labels have been used, among them, paranodal rhythms,[16] parasinus rhythms,[17] and coronary sinus rhythms.[18] All these terms imply that the impulse arises near the A-V node rather than the S-A node. Since such impulses have a short distance to travel before reaching the A-V node, these workers ascribe the shortening of the P-R interval to the shortened conduction time. The theory of the low ectopic auricular focus is based on the belief that the configuration of the P wave in the standard leads is not influenced by the location of the pacemaker in the auricle, but rather by the direction of spread of the impulse from the ectopic focus to the A-V node.

It has been clearly demonstrated that a caudad auricular pacemaker would be manifested by an inverted P wave in leads II and III.[7] Thus the upright P waves in our cases, both clinical and experimental, are not of low auricular origin. Moreover, since the rate of auricular depolarization averages about 1000 mm. per second,[19] it is estimated that activation of the A-V node occurs 0.05 to 0.06 second after depolarization of the sinoauricular node. Thus, shortening of the P-R interval by more than 0.04 to 0.05 second could not occur even if the impulse were initiated as close to the A-V node as possible.

A wandering auricular pacemaker, whether or not associated with transient nodal rhythm, will manifest itself by different configuration of the P waves in the standard leads and by shortening of the P-R interval. A wandering pacemaker obviously did not occur in our cases, as the P wave remained unaltered.

Ventricular Type of Short P-R Interval. Others have stressed the possibility that a hyperexcitable septal or ventricular focus is prematurely discharged under the mechanical or electrical influence of auricular systole.[4] This would explain the short P-R interval and the QRS complex of long duration and abnormal configuration, comparable to an extrasystolic complex. This theory is based on neurophysiologic principles and is supported by experimental observations in animals and in humans. Such complexes have been produced by injection of alcohol, adrenaline or silver nitrate into the septum,[20] by mechanical stimulation of the anterobasal part of the septum,[21] and by injection of strychnine into the wall of the ventricular myocardium[22]; in fact, they have been produced by electrical, mechanical and chemical stimulation of any part of either ventricle.[7] In human subjects anomalous atrioventricular excitation has been produced by stimulation of the ventricular septum during cardiac catheterization.[23, 24] Variants of the theory of the idioventricular complex have been proposed, such as is-

rhythmic dissociation,[25] "phénomène d'accrochage"[25b] and regular interference between auricular and ventricular foci.[26]

There is no question that complexes of this type occur when the ventricle is stimulated from any ventricular focus. In our experience this is of frequent clinical occurrence. In these cases, a very long electrocardiographic strip must be taken. Although many, or most, of the aberrant beats will be preceded by P waves, one will find QRS complexes without preceding P waves. In other words, these patients frequently have ventricular extrasystoles and ventricular tachycardia. These aberrant QRS complexes will have the same configuration as the QRS complexes associated with the short P-R interval. The configuration of the aberrant QRS complex depends upon which ventricle is stimulated first: In lead I, the major ventricular deflection will be inverted if the left ventricle is stimulated and upright if the right ventricle is stimulated. It is possible that the aberrant QRS complexes and the short P-R interval in case 7 were of this type, because in other electrocardiograms similar aberrant QRS complexes occurred without preceding P waves.

In the experiments reported in this paper, great care was taken not to stimulate the ventricle during the procedure, and all recorded QRS complexes were preceded by P waves.

Aberrant Anatomic Pathways. For more than 20 years, the existence of one or more muscular or neuromuscular accessory bridges, extending from the auricle to the ventricular myocardium, has been the most generally accepted physiopathologic explanation for the occurrence of short P-R intervals with normal or abnormal QRS complexes.

The termination of the aberrant pathway in the ventricular myocardium would short-circuit the delaying A-V node and cause precipitation of the affected ventricle. The terminal phase of ventricular systole would be the result of the impulse traveling along the normal auriculoventricular pathway. A shorter P-R interval associated with an aberrant QRS complex would thus be produced.

The pattern of short P-R intervals with QRS complexes of normal duration is identified as a variant Wolff-Parkinson-White syndrome by only a few workers.[3, 27, 28] They base their interpretation on a few scattered observations of abnormal pathways terminating in the interventricular septum,[3, 29, 30] so located as to permit the impulse to bypass the A-V node and motivate the common bundle of His. Stimulation of the ventricles thus would follow the normal sequence, yielding a QRS complex of normal duration.

The following evidence has been presented in support of the theory of anomalous atrioventricular conduction: Histologic examination of the auriculoventricular groove in a few clinical cases of Wolff-Parkinson-White syndrome revealed the presence of aberrant muscle bundles connecting the auricle and the ventricle.[3, 31, 32] These reports constitute the major basis for the wide acceptance of the theory of anomalous atrioventricular conduction. The ingenious experiments of Butterworth and Poindexter[33] suggested the functional significance of such an aberrant pathway. They established an electrical circuit between the auricle and the corresponding ventricle in dogs and cats; a typical Wolff-Parkinson-White complex was produced by the application of electrical current to the ventricle.

It should be pointed out that, in some clinical cases of Wolff-Parkinson-White syndrome, no aberrant pathways could be demonstrated histologically.[34, 35] On the other hand, aberrant connections have been found in the normal heart in a variety of species.[38] In a patient with the Wolff-Parkinson-White syndrome, there is, thus far, no way of ascertaining that an anomalous anatomic connection, if present, is responsible for the syndrome. Despite the lack of direct evidence, the theory has gained wide acceptance, principally because it explains beautifully the abnormal complexes.

Accelerated Conduction. As a result of the demonstration that the function of the A-V node is to delay the transmission of the impulse from auricle to ventricle,[2] it was theorized that, if this function could be altered, the impulse might not be delayed to the same

extent; the P-R interval would thereby be shortened.[7]

The A-V node was altered by a continuous, subthreshold, direct electrical current applied to the node. It was observed that the P-R interval became shortened and the QRS complex aberrant and widened. Since the QRS complex was abnormal but the last portion usually occurred at the normal time, it was suggested that only part of the node discharged prematurely and the remainder after a normal delay. As the essential disturbance was premature transmission of part of the impulse through the A-V node, the term accelerated auriculoventricular conduction, or accelerated conduction, was utilized to describe this phenomenon.[7]

Antagonism of Complete Heart Block and Accelerated Conduction

Complete heart block should be a means of determining the validity of the aberrant bundle theory or the acceleration conduction theory. According to the theory of accelerated auriculoventricular conduction, complete heart block and accelerated conduction are mutually exclusive. According to this theory, the abnormality lies in the specific auriculoventricular pathway. If this pathway is completely destroyed, as in *complete* heart block, accelerated conduction obviously cannot occur. According to the bundle of Kent theory, complete heart block should not interfere with, but should actually facilitate, the production of accelerated conduction. The explanation is that, since the normal pathway is destroyed, the aberrant pathway should function unopposed.

It has been clearly shown in animals that complete A-V block and accelerated conduction cannot occur at the same time: (1) In a previous study in seven animals, Wolff-Parkinson-White complexes could not be produced by electrical stimulation of the endocardial surface of the right ventricle after the production of complete heart block by destruction of the bundle of His (ventricular type of Wolff-Parkinson-White mechanism).[7] (2) In the present study, accelerated conduction complexes could not be reproduced by any of the methods after complete heart block had developed as a result of manipulation of the A-V node. (3) After the animal recovered from complete heart block, accelerated conduction complexes occasionally occurred.

Clinically, also, it appears that complete heart block and a Wolff-Parkinson-White complex are mutually exclusive. Two cases in point have been reported. The first case, reported by Coelho,[36] concerns a 62 year old woman with hypertension. The electrocardiogram taken after posterior myocardial infarction revealed 2:1 heart block associated with short P-R intervals and abnormal QRS complexes. Subsequently complete heart block developed, after which accelerated conduction or Wolff-Parkinson-White complexes were no longer recorded. In the second case, reported by Fox and associates,[37] Wolff-Parkinson-White syndrome was diagnosed in a 70 year old woman. After the intravenous administration of 300 mg. of Pronestyl, 2:1 A-V block developed, associated with Wolff-Parkinson-White complexes of the conducted impulses. After an additional intravenous dose of 200 mg., complete heart block occurred and the Wolff-Parkinson-White beats disappeared.

In view of the above experimental and clinical evidence, it seems probable that the short P-R interval results from accelerated conduction rather than from an anomalous anatomic auriculoventricular pathway. Further observations of clinical cases manifesting short P-R intervals which become complicated by complete heart block are desirable.

It may be recalled that Kent claimed, "When in the heart of the mammal one severs all the structures which connect the auricles to the ventricles with the exception of a strip of tissue on the right lateral aspect of the organ, spontaneous beats arising in the auricle still pass through the ventricle and evoke ventricular beats."[38] Erlanger, whose classic studies[39] early in the century established the nature of heart block, strenuously objected[40] to Kent's idea of a functional aberrant connection between auricle and ventricle. He clearly showed that when the bundle of His was crushed, though all other connections were untouched, heart block occurred. When the crush was placed elsewhere, heart block never occurred.

In this laboratory, in this and in previous studies over the past four years, A-V nodal function has been completely destroyed in more than 60 animals. We have never failed to produce complete heart block. As Erlanger has commented, if there were anomalous connections, permanent anomalous ventricular activation should have been established immediately after the node was destroyed. It should also be pointed out that extensive postmortem observations over the past 50 years have shown that chronic A-V block in man occurs only in the presence of a lesion in the region of the A-V node and bundle of His.

Kent's physiologic observations, as far as we know, have never been confirmed. Recently Frau, Maggi and Agostini repeated Kent's experiments in the rat.[41] They also severed all connections between the auricle and the ventricle except for a strip of tissue on the right lateral aspect of the heart. Their results were entirely negative, and they concluded that there was no functioning anomalous anatomic pathway.

From extensive physiologic and pathologic data accumulated during the past half-century, as well as some clinical data, it becomes apparent that the theory of anomalous functioning A-V connections has comparatively little evidence to support it. Furthermore, observations on complete heart block clearly indicate that the A-V node and the bundle of His are necessary not only for transmission of the normal impulse from auricles to ventricles, but for the production of the accelerated conduction complexes in animals and probably in man.

Partial Heart Block and Accelerated Conduction

In distinction to *complete* heart block, it has been shown that *partial* heart block and accelerated conduction can occur simultaneously. Figures 11 and 12 illustrate concomitant 2:1 heart block and accelerated conduction. Several reports of identical manifestations in clinical cases have been published.[30, 36, 42]

In the present series of experiments we have observed repeatedly, after injecting the A-V node, complete heart block without accelerated conduction complexes. After absorption of injected material, there is a gradual return to lesser degrees of heart block, occasionally associated with accelerated conduction complexes. After absorption of injected material, there is a gradual return to lesser degrees of heart block, occasionally associated with accelerated conduction complexes. A clinical case with similar manifestations has been reported. The patient was a 59 year old man with known hypertension of many years' duration. Electrocardiograms showed a normal P-R interval. Following a second episode of posterior myocardial infarction, the electrocardiograms showed second degree heart block, which was succeeded by first degree heart block during the convalescent stage. The P-R interval eventually reverted to normal. Several months later, in the absence of any new clinical manifestations, the electrocardiogram exhibited accelerated conduction, with the P-R interval measuring 0.09 second. Autopsy disclosed extensive replacement fibrosis in the region of the A-V node.[7]

The presence of *partial* heart block indicates disturbance of A-V nodal function. Since partial heart block and accelerated conduction complexes were observed in the same animal, the indication is that a single lesion in the A-V node may result in both types of disturbance. Partial heart block and accelerated conduction may occur in the same patient (cases 4 and 5). If the A-V node is completely destroyed, complete heart block results. If it is partially disturbed, partial heart block results. However, the disturbance may on occasion be such, as in some patients and in these experiments, that the function of normal delay is impaired and accelerated conduction results. Thus, if the node is diseased but not completely destroyed, the impulse may at times be delayed and at other times accelerated. The mechanism by which the A-V node at one time delays and at other times accelerates conduction in the same heart is unknown.

The A-V Node, the "Central Nervous System" of the Ventricle

It has been shown that when a constant subthreshold stimulus was applied to the A-V node, ventricular aberration of a constant type occurred. When other parts of the node were similarly stimulated, entirely different types

of ventricular complexes resulted. This suggested that the node is a sort of "central nervous system" and that, from a physiologic viewpoint, certain parts of the node supply specific parts of the ventricle.[7] Mechanical stimulation of the A-V node has yielded aberrant ventricular complexes similar to both right and left ventricular extrasystoles and bundle-branch block.[43] Further evidence supporting this idea was obtained by Smith and co-workers,[44] who showed that strategically placed cuts in the endocardium could produce segmental block with no change in the rest of the ventricles.

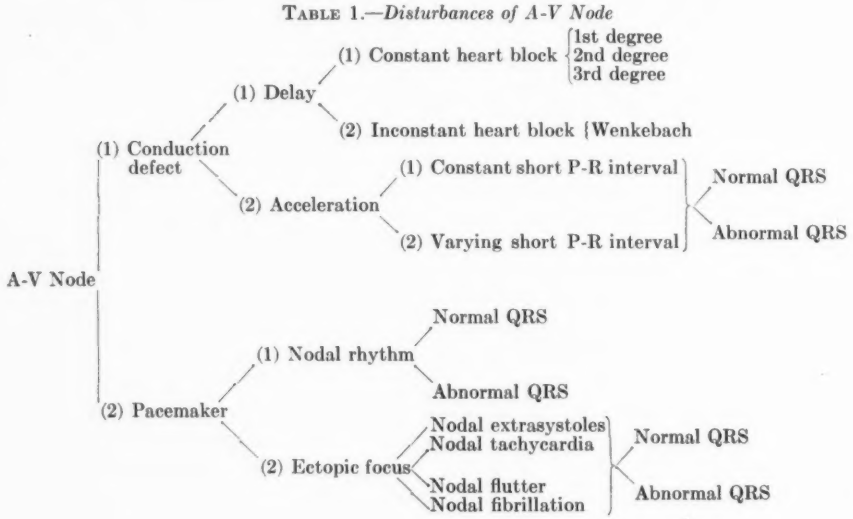
In this study, after chemical modification of the node, it was observed that the QRS complex associated with the short P-R interval was either of normal duration or aberrant and widened. It is suggested that when it is widened, one part of the node is discharged early while the rest of the node is discharged at its normal time. The part of the node which is discharged early determines the form of the initial portion of the QRS complex. The normal QRS, it is postulated, occurs when the entire node discharges synchronously, resulting in normal sequence of activation of the ventricles. Whether the nodal changes produced in our experiments represented specific effects of the drugs injected or nonpharmacologic effects cannot be stated at present. In either event, the results of the experiments are attributed to alteration of nodal function.

Indirect evidence has been obtained that afferent impulses from any part of either ventricle may be conducted through the A-V node to the auricle.[7] The ventricular type of accelerated conduction can be explained by this mechanism. Retrograde conduction may be considered a crude example of this phenomenon. More work on the physiology of the A-V node is obviously necessary.

Classification of A-V Nodal Abnormalities

The multiplicity of disturbances produced by experimental procedures directed at the A-V node suggests that this region has a more important role in regulating the heart beat than hitherto supposed. A tentative classification of A-V nodal dysfunctions appears in table 1. Normally the A-V node delivers the auricular impulse to the ventricles after a delay of 0.07 to 0.15 second. An alteration of this function would produce either of two main electrocardiographic abnormalities: (1) various degrees of A-V block, or (2) accelerated conduction with shortening of the P-R interval. It is postulated that simultaneous activation of the entire node yields normal QRS complexes, while premature or delayed activation of parts of the node produces QRS aberrations similar to those produced by

TABLE 1.—*Disturbances of A-V Node*



ventricular pacemakers. Occasionally the A-V node conducts in a retrograde fashion. This may be associated with delay of the impulse and with some degree of retrograde block (case 4). The A-V node may also initiate the impulse as in A-V nodal rhythm and nodal arrhythmias. It is postulated that these disturbances may occur without histologically demonstrable lesions of the nodal tissue, as in one of our cases, or may be associated with demonstrable pathology, as in three previously reported cases.[7] It is suggested that the well-known Wolff-Parkinson-White syndrome is an example of accelerated conduction with ventricular aberration. This condition is often associated with nodal beats and nodal arrhythmias. Whether or not organic changes are present in such cases is not yet known.

It seems remarkable that by altering the A-V node—a tiny structure less than 2 mm. in diameter—by chemical, mechanical or electrical stimulation, so many abnormalities may be produced. It is perhaps not quite so remarkable if one compares the heart with the central nervous system, where very small lesions, if strategically located, may cause profound changes. Much larger lesions in so-called silent areas in the brain or in the heart may cause no signs or symptoms.

Summary and Conclusions

1. Seven clinical cases with electrocardiographic patterns characterized by a short P-R interval are reported. The short P-R interval was of constant or of varying duration. The QRS complex was either normal or aberrant. The abnormality can occur in normal subjects with no evidence of organic heart disease or may occur as a result of organic heart disease. Nodal rhythm and partial heart block occurred in some of the cases. These cases are not the classic Wolff-Parkinson-White syndrome.

2. In 40 dogs, the A-V node was injected with cocaine, formaldehyde or acetylstrophanthidin. Eleven of the dogs developed exactly the same variety of P-R and QRS abnormalities seen in the seven clinical cases. Heart block and nodal rhythm occurred in the other animals.

3. In 10 animals, control injections into other parts of the heart did not produce any of the above-mentioned electrocardiographic phenomena.

4. The normal function of the A-V node is to delay passage of the impulse from the auricle to the ventricle. This delay accounts for the major portion of the normal P-R interval. It is thought that the injections interfered with this function, allowing acceleration of conduction from auricle to ventricle with resultant shortening of the P-R interval. The abnormality has been termed *accelerated conduction*.

5. Since the electrocardiograms in the patients and in the dogs were identical, it is proposed that the abnormality in the patients may also have been due to disturbance of the A-V node.

6. Evidence has been presented that the A-V node is a sort of "central nervous system" of the heart and that, from a physiologic viewpoint, certain parts of the node supply specified parts of the ventricle.

7. In cases with short P-R intervals, it is postulated that when the entire A-V node is discharged prematurely, the QRS is narrow and normal. If only part of the node is discharged prematurely, and the rest discharged later, then the QRS is wide and aberrant.

8. The two major theories of the short P-R interval phenomenon are (1) anomalous anatomic pathways and (2) accelerated conduction through the normal pathway. The phenomenon of complete heart block should be a means of determining which theory is valid. If the short P-R interval is due to anomalous pathways, then, after destruction of the A-V node, the abnormal beats should be accentuated and permanent. If the abnormal beats are due to dysfunction of the normal conducting system, destruction of the normal system should eliminate these beats.

9. It has been demonstrated that complete heart block can always be produced by a small lesion in the A-V node in both man and animals. It seems unlikely that the aberrant anatomic pathways which have been described can have a physiologic function, since they do not function even after the A-V node is destroyed.

10. In all experiments in this series, complete heart block eliminated all the accelerated conduction phenomena in the dogs. Two clinical cases have been reported in which Wolff-Parkinson-White complexes disappeared after production of complete heart block. This is evidence in favor of the accelerated conduction theory and against the anomalous anatomic pathway theory.

11. *Complete* heart block and accelerated conduction are mutually antagonistic. This is not true of *partial* heart block, which may coexist with accelerated conduction. This has been found in our experimental animals and has been reported to occur in patients. It is postulated that in such cases the A-V node is diseased, blocking some beats and transmitting others prematurely.

12. As a result of simultaneous recording of direct auricular and limb leads, it was found that the P-R interval in the limb lead may be so short that the P wave is buried in the initial portion of the upstroke of the QRS complex. Such beats may be erroneously diagnosed as idioventricular beats, ventricular extrasystoles or ventricular tachycardia. In fact, such beats may be manifestations of extreme accelerated conduction.

13. A clinical classification of disturbances of the A-V node is presented. It is suggested that the well-known Wolff-Parkinson-White syndrome is due to an abnormality of the A-V node resulting in short P-R intervals, aberrant QRS complexes, and occasionally nodal rhythms and arrhythmias.

14. The A-V node, a very minute structure, thus can have three different types of disturbances: (a) heart block, (b) accelerated conduction and (c) nodal rhythms and arrhythmias. Dysfunction of the A-V node may also completely change the duration and configuration of the QRS complex.

Summario in Interlingua

Es reportate 7 casos de configurationes electrocardiographic a breve intervallos P-R de natura o constante o variabile. Le complexo QRS esseva o normal o aberrante. Iste anormalitates esseva reproducite experimentalmente in canes per le injection de varie drogas a in le region del nodo atrioventricular. Es discutite le theorias que ha essite formulate pro explicar le presente phenomenos. Le resultatos indica que un acceleration del conduction in le nodo atrioventricular es responsabile pro le breve intervallo P-R. Le forma del complexo ventricular pote depender del activitate synchrone o asynchrone del nodo atrioventricular. Nos presenta un classification de dysfunctionamentos del nodo atrioventricular.

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Left Ventricular Hypertrophy

A Study of the Accuracy of Current Electrocardiographic Criteria When Compared with Autopsy Findings in One Hundred Cases

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The current electrocardiographic criteria for the diagnosis of left ventricular hypertrophy have been analyzed in 100 cases of pure left ventricular hypertrophy proved at autopsy. Only those cases were used in which the greatest thickness of the left ventricle was 13 mm. or more, the right ventricle did not exceed 4 mm. in thickness, and the heart weight exceeded the upper limit of the expected normal. Also, only those cases were studied on whom multiple lead electrocardiograms were available. Conclusions are presented as to which sets of electrocardiographic criteria give the greatest accuracy in the diagnosis of left ventricular hypertrophy.

LEFT ventricular hypertrophy has long been known to give rise to certain characteristic changes in the electrocardiogram. The findings in the standard leads upon which this diagnosis is made have been well described.[1-3] These patterns consist essentially of the presence of left axis deviation with an increase in the amplitude of the QRS complex, the size of R_1 and S_3 exceeding 2.5 millivolts, or with depression of the S-T segment in lead I, or with a T wave in lead I of 1 mm. or less.[1] Barnes[2] has described what he calls the typical pattern of left ventricular strain. This consists of left axis deviation with S-T segment depression in lead I and a negative T wave with a convex contour to the anterior limb; reciprocal changes are seen in lead III. Distinction between the terms hypertrophy and strain has been suggested,[1, 4] using the term hypertrophy when left axis deviation and high voltage are present, and strain when the characteristic changes occur in the S-T segment and T wave in the absence of high voltage or left axis deviation. Others[2, 5, 6] however, use the terms left ventricular strain and hypertrophy synonymously.

It has frequently been pointed out that left ventricular hypertrophy may occur with either normal axis or even right axis deviation in the standard leads, depending upon the heart position.[1, 5, 7, 8, 9] It was desirable, therefore, to have additional electrocardiographic means of determining left ventricular hypertrophy.

Wilson and his associates,[9, 10] by using the precordial leads, set down additional criteria obtained from these leads; namely, the peak of the R waves in leads V_5 and V_6 is abnormally late and the deflection is abnormally tall. The QRS interval in these leads is often 0.10 or 0.11 second in duration and occasionally even 0.12 second. The R waves in leads V_1 and V_2 are small and the S waves are large. In more than one-half the cases Q waves occur in V_5 and V_6 and the T waves are frequently inverted. More recently Sokolow and his co-workers,[11] in a study of 147 patients with the clinical diagnosis of left ventricular hypertrophy, have suggested additional criteria for the electrocardiographic diagnosis of left ventricular hypertrophy. Others[4, 12, 13] have offered even different criteria for the diagnosis of left ventricular hypertrophy based on findings in the unipolar extremity leads.

Noth, Myers, and Klein[14] analyzed the findings in the precordial leads in 84 cases of

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pathologically proved left ventricular hypertrophy. They found that differentiation between the pattern of left ventricular hypertrophy and of normal subjects could not be made from the amplitude of the R waves in V_5 and V_6. Thirty-four of the 84 cases studied showed an abnormal Q-R and/or R duration.

Lewis[7] in 1914 and Herrmann and Wilson[8] in 1922 correlated the weight of the left ventricle with the electrocardiographic changes in the standard leads in cases of ventricular hypertrophy.

To our knowledge there has been no recent attempt to correlate the autopsy findings in cases of pure left ventricular hypertrophy with the 12-lead electrocardiogram. The present study was undertaken in order to determine which of the present sets of diagnostic criteria give the greatest accuracy when compared with the autopsy findings.

Methods and Materials

The autopsy protocols of the Pathology Department of the Cincinnati General Hospital* from 1949–1951 were examined and all cases with a left ventricular thickness of 13 mm. or more and a heart weight of more than the expected normal for the length of the body[15] were collected. Any case which had, in addition, a right ventricular thickness of more than 4 mm. was not included because in the present study we were concerned only with the diagnosis of left ventricular hypertrophy. The left ventricle was opened in the Pathology Department by a longitudinal incision along the anteroseptal portion (at right angles to the epicardial surface) carried around the apex and along the posteroseptal portion. The greatest thickness of the cut surface was measured from the epicardium to endocardium but care was taken not to include the thickness of the papillary muscles. The measurements were made by different prosectors but the technic was uniform; however, an allowable error of ± 2 mm. was accepted as a definite possibility. Therefore, although most pathologic criteria[16, 17] take 10 or 12 mm. as the upper limits of normal we chose 13 mm. in order to be reasonably certain that through inaccuracy in measurement we were not including any normal hearts.

After collecting all cases satisfying these criteria the electrocardiographic files were reviewed and only those cases on whom multiple lead electrocardiograms were available were studied. Cases of left bundle-branch block, right bundle-branch block, or those with pathologic evidence of myocardial infarction were not included. The measurements from the electrocardiograms were carefully made, utilizing a hand lens when necessary. Upward deflections were measured from the top of the base line to the peak of the upstroke; downward deflections were measured from the bottom of the base line to the nadir of the downstroke. If there were variations in the height of a deflection due to respiratory variations, an average of several deflections was used. The RS-T segment deflections were measured from the isoelectric level except in those cases where, because of tachycardia (rate over 100) or first degree A-V heart block, the P wave was superimposed on the preceding T wave and no true T-P level was obtained; in these cases RS-T segment shifts were measured in relation to the P-Q segment. The height of upright T waves in cases with depressed RS-T segments was measured from the level of the RS-T segment (rather than from the isoelectric line).

The electrocardiographic position of the heart was noted, using Wilson's criteria.[10]* The last electrocardiogram taken before death was used in cases in which many tracings were available except in occasional cases where the last record was technically unsatisfactory.

Results

Criteria of Gubner and Ungerleider

Gubner and Ungerleider[1] have set down the following criteria for the diagnosis of left ventricular hypertrophy from the standard leads, namely, the occurrence of left axis deviation with: (1) R_1 plus S_3 exceeding 25 mm., or (2) depression of the S-T segment of 0.5 mm. or greater in lead I, or (3) a T wave in lead I of less than 1 mm.

Thirty-six of the 100 cases satisfied their criteria of left axis deviation with high voltage and S-T segment or T-wave abnormalities (table 1).

Criteria of Katz

Katz[5] uses the term left heart strain synonymously with left ventricular hypertrophy. He classifies left heart strain into four groups: first type, second type, mixed type, and concordant type.

In the first type, there is left axis deviation, and the S-T segments and T waves are normal;

* A few cases from the files of the Jewish Hospital and from the Christian R. Holmes Hospital were also reviewed.

* In the study of Goldberger's criteria for ventricular hypertrophy, his criteria for rotation around the anteroposterior axis were used.

TABLE 1.—*Gubner and Ungerleider*

		(1)	(2)	(3)	
No. Cases	LAD	$R_1 + S_3$ >25 mm.	S-T_1 ↓ 0.5 mm. or >	T_1 <1 mm.	LAD + (1), (2), or (3)
100	55	8	16	52	36

36 Per Cent Accuracy

lead II consists of a small, equiphasic QRS complex, or a complex with a deep S wave.

The second type consists of left axis deviation with S-T segment depression in lead I with upward convexity of the segment and T-wave inversion.

In the mixed type, there is left axis deviation with a small equiphasic QRS complex in lead II or a complex with a deep S wave, and S-T-T changes in lead I such as those observed in type II.

In the concordant type, the QRS complexes are upright in the standard leads, and there is S-T segment depression and T-wave inversion in lead I (and II, III).

Katz also describes characteristic changes in the chest leads, namely, a QS in CF_2 or an R wave of less than 1.5 mm., S-T segment elevation in CF_2 of more than 2.5 mm., and an upright T wave; in CF_5 the S-T segment is depressed and the T wave inverted.

Using Katz's criteria for the standard leads we found 40 per cent accuracy. If we add his criteria for the chest leads this increases the accuracy to 59 per cent (table 2).

Criteria of Schach, Rosenman, and Katz

Schach, Rosenman, and Katz[12] found that criteria indicative of left ventricular strain included a negative deflection in aV_R greater than 14 mm., an R wave in aV_L exceeding 12 mm., an R wave in aV_F exceeding 19 mm., and a value for the sum of the negative deflection in aV_R and the positive deflection in aV_L or aV_F exceeding their maximum normal.

TABLE 2.—*Katz (100 Cases)*

Type I LAD Deep S_2 S-T-T Normal	*Type II* LAD S-T-T_1 ↓	*Mixed* LAD Deep S_2 S-T-T_1 ↓	*Concordant* QRS Upright S-T-T ↓ $_{1(2,3)}$	$\frac{CF_2\ (V_2)}{QS}$ R < 1.5 mm. S-T ↑ > 2.5 mm. T ↑	$CF_5\ (V_5)$ S-T-T ↓
12	11	9	8	8	11

40 Per Cent Accuracy

59 Per Cent Accuracy

TABLE 3.—*Schach, Rosenman, and Katz*

Heart Position	No. Cases	aV_R Neg. > 14	aV_L R > 12	aV_F R > 19	Neg. aV_R + pos. aV_L (aV_F) > max. normal	Total Positives
V	13	1	—	1	3 (29)	3
SV	9	0	—	0	0 (23)	0
I	29	7	3	1	8 (26)	8
SH	9	0	0	—	0 (22)	0
H	36	1	6	—	6 (21)	10
Total..	96	9	9	2	17	21

21
+13 with ↑T aV_R
34 (35 per cent)

If we combine these criteria with those of Katz for standard and chest leads, we get 59 + 8 = 67 per cent.

Twenty-one of our cases satisfied these criteria. If, in addition, an elevated S-T segment or an upright T wave in aV_R is included, the accuracy increases to 35 per cent (table 3).

If we combine these criteria for the unipolar extremity leads with those of Katz[5] for the standard and chest leads, we get an accuracy of 67 per cent (table 3).

Criteria of Goldberger

Goldberger[4] has pointed out that left ventricular hypertrophy may occur with a normal

TABLE 4.—*Goldberger*

Horizontal				
No. Patients	Hypertrophy Rav_L 13 or >	Strain ST-T ↓ and/or prolonged Q-T in aV_L	Hyper. + Strain	Total Positives
73	2	37	9	48
Vertical				
No. Patients	Hypertrophy Rav_F 20 or >	Strain ST-T ↓ and/or prolonged Q-T in aV_F	Hyper. + Strain	Total Positives
25	0	18	1	19

67 of 98 Patients—68 Per Cent Accuracy

TABLE 5.—*Goulder and Kissane*

Heart Position	No. Cases	aV_L		
		R > 11 T/R < 10%	R > 11 T/R > 10%	R 10-11 T/R < 10%
Semi Hor.....	9	0	0	0
Hor.....	36	7	2	3
Total.....	45	7	2	3

12 of 45 Cases—27 Per Cent Accuracy

electrocardiogram, or with high voltage in the unipolar extremity leads (R in aV_L of 13 mm. or more in a horizontal heart, or R in aV_F of 20 mm. or more in a vertical heart). He uses the term left ventricular strain when there is RS-T segment depression and/or T wave inversion and/or prolongation of the Q-T in aV_L in a horizontal heart or in aV_F in a vertical heart. If both high voltage and ST-T changes coexist he speaks of left ventricular hypertrophy and strain.

Utilizing his criteria for the unipolar extremity leads we found an accuracy of 68 per cent* (table 4).

Criteria of Goulder and Kissane

Goulder and Kissane[13] have proposed criteria for the diagnosis of left ventricular hypertrophy in horizontal or semihorizontal hearts. Based upon the height of the R wave and the T to R ratio in aV_L, they found that 83 per cent of their 65 patients had an R wave in aV_L greater than 11 mm. with or without a T to R ratio less than 10 per cent or an R wave over 10 mm. always with a T to R ratio less than 10 per cent.

There were 12 of 45 cases (with horizontal or semihorizontal hearts) that could be diagnosed by utilizing their criteria, an accuracy of 27 per cent (table 5).

* Goldberger states that the changes characteristic of left ventricular hypertrophy (high voltage) or strain (ST-T changes) also occur in one or more precordial leads which face the epicardial surface of the left ventricle (V_4, V_5, and V_6). He states, in addition, that these precordial leads may show widening of the QRS, or delay in the onset of intrinsicoid deflection. Since these same criteria have been previously suggested by other authors[9, 10, 11] they were not separately analyzed. Instead, analysis of Goldberger's proposed criteria has been limited to the unipolar extremity leads.

TABLE 6.—*Noth, Myers, and Klein*

No. Cases	V_5, V_6 R 0.04 sec. or >	V_5, V_6 Q − R 0.05 sec. or >	Total
100	14	24	28

Criteria of Noth, Myers, and Klein

Noth, Myers, and Klein[14] found an abnormal Q-R (0.05 second or more) duration and/or an abnormal R duration (0.04 second or more) in V_5, V_6 in 34 of their 84 cases of pathologically proven left ventricular hypertrophy.

We encountered these findings in 28 per cent of the present series (table 6).

Criteria of Wilson and Co-workers

Wilson and associates[9, 10] have pointed out that the precordial leads in left ventricular hypertrophy differ from the normal in the following characteristics: (1) the R waves in V_1 are abnormally small (1 mm. or less) and may be absent[18]; the S waves are abnormally large (24 mm. or more)[18]; (2) the transition zone is often displaced to the left; (3) in V_5 and V_6 the peak of R is abnormally late (0.05 second or more)[18]; (4) the R waves in V_5, V_6 are abnormally tall (33 mm. or more in V_5, 26 mm. or more in V_6)[18]; (5) the T wave is often inverted in V_5 and V_6; (6) the QRS interval is frequently increased to 0.10 or 0.11 second.

One or more of these criteria were present in 81 per cent of our cases (table 7). If one requires a minimum of two of these criteria to be present, the positivity declines to 53 per cent; if three criteria are required the positivity diminishes to 18 per cent.

Criteria of Sokolow and Lyon

Sokolow and Lyon[11] have formulated the following criteria for the diagnosis of left

TABLE 7.—*Wilson's Criteria (100 Cases)*

V_1			V_5				V_6				
R 1 mm. or <	S 24 or >	Trans. Zone Displaced to Left	Q Present	R 33 mm. or >	Onset of I.D. 0.05 sec. or >	T ↓	Q Present	R 26 mm. or >	Onset of I.D. 0.05 sec. or >	T ↓	QRS 0.10 or 0.11 sec.
56	11	36	34	3	19	20	37	13	20	18	14

One or more of these criteria present in 81 cases

TABLE 8

A. Sokolow and Lyon's Criteria for Unipolar Extremity Leads

No. Cases	aV_R	aV_L			aV_F		
	T↑	R >11 mm.	RS-T↓ >0.5 mm.	T Low or ↓ +R 6 mm. or > +RS-T↓	R >20 mm.	RS-T↓ >0.5 mm.	T Low or ↓ +R 6 mm. or > +RS-T↓
99	21	11	10	5	2	15	7

47 Per Cent Accuracy

B. Sokolow and Lyon's Criteria for Precordial Leads

No. Cases	V_5					V_6					R/T 10 or > in V_5, V_6	R/S in V_5 / R/S in V_1 > 100	R in V_5 (V_6) + S in V_1 >35 mm.
	R > 26 mm.	RS-T↓ > 0.5 mm.	T low or ↓	Onset of I.D.		R > 26 mm.	RS-T↓ > 0.5 mm.	T low or ↓	Onset of I.D.				
				0.05 sec. or >	>0.05 sec.				0.05 sec. or >	>0.05 sec.			
100	18	34	46	19	6	13	29	47	19	7	26 (of 73 with ↑T) 36%	19 (of 61) 31%	28

At least one of these criteria present in 75 cases. Unipolar + Precordial Leads: 85 per cent Accuracy

ventricular hypertrophy from the unipolar extremity leads: (1) RS-T segment depressed more than 0.5 mm. in aV_L or aV_F; (2) flat, diphasic, or inverted T waves, with an R wave of 6 mm. or more in aV_L or aV_F and item 1; (3) voltage of R wave in aV_L greater than 11 mm. or in aV_F greater than 20 mm.; (4) upright T wave in aV_R.

Employing these criteria we found 47 per cent accuracy in our series (table 8*A*). Seven cases were diagnosed by the unipolar extremity leads alone.

Sokolow and Lyon[11] described the following changes in the precordial leads in left ventricular hypertrophy: (1) the RS-T segments are depressed and the T waves low or inverted in V_5 or V_6; (2) R waves in V_5 or V_6 exceed 26 mm.; (3) the onset of the intrinsicoid deflection in V_5 or V_6 exceeds 0.05 second*; (4) the R to T ratio in V_5 (or V_6) is 10 or greater; (5) the R to S ratio in V_5 divided by the R to S ratio in V_1 is greater than 100; (6) the sum of the R wave in V_5 (or V_6) and the S wave in V_1 exceeds 35 mm.

Using these criteria for the precordial leads we found an accuracy of 75 per cent in our series (table 8*B*).

Combining Sokolow and Lyon's criteria for the unipolar extremity leads and the precordial leads we found 85 per cent accuracy. If we require two or more criteria to be present the accuracy declines from 85 per cent to 64 per cent.

Effect of Digitalis on the Accuracy of Diagnosis of Left Ventricular Hypertrophy

Digitalis is known to produce S-T-T changes which at times may be indistinguishable from those of left ventricular hypertrophy. In our series there were 33 patients who were receiving

TABLE 9.—*Effect of Digitalis Administration upon Accuracy of Criteria*

Authors	Total No. of Positives	No. of Positives Excluding Those Obscured by Digitalis
Gubner and Ungerleider	36	25
Schach, Rosenman, and Katz	34	29
Goldberger	67	50
Katz	59	45
Sokolow and Lyon	85	73
Wilson and colleagues	81	79
Noth, Myers, and Klein	24	24

* Since Sokolow and Lyon found 58 per cent of their cases with left ventricular hypertrophy to have a ventricular activation time of 0.05 to 0.08 second, we have also analyzed our cases to include those with an onset of the intrinsicoid deflection of 0.05 second or greater.

TABLE 10.—*Cases Missed by All Authors' Criteria*

Case No.	RV (mm.)	LV (mm.)	Heart Wt. (Gm.)	% Heart Wt. above Normal	ECG Diagnosis
1	3	15	435	15	Normal
2	4	16	400	5	Normal

digitalis. We have compared the accuracy of the various authors' criteria after arbitrarily excluding those instances where the diagnosis rested on S-T-T alterations alone. As shown in table 9 almost all the authors' criteria suffered.

Digitalis shortens the Q-T interval, whereas left ventricular hypertrophy is reported to prolong the Q-T interval.[4, 6, 19, 20, 21] We have measured the Q-T interval in our 100 cases. Sixty-seven cases did not receive digitalis; 29 (43.3 per cent) had a normal Q-T interval while 38 (56.7 per cent) showed a prolonged Q-T interval. Thirty-three cases received digitalis; 22 (66.7 per cent) had a normal Q-T while only 11 (33.3 per cent) showed a prolonged Q-T interval. Thus, although more than one-half of our cases with left ventricular hypertrophy who were not receiving digitalis had abnormally long Q-T intervals, only one-third of those who were receiving digitalis had prolonged Q-T intervals.

Analysis of Cases Missed by Current Electrocardiographic Criteria

There were two cases in which hypertrophy was missed by all authors' criteria. The salient features of these are shown in table 10.

There were four cases in which hypertrophy was missed by the criteria of Sokolow and/or Wilson, but three of these were diagnosed by Katz's criteria and one by Goldberger's criteria. These are shown in table 11.

TABLE 11.—*Cases Missed by Criteria of Wilson and/or Sokolow and Diagnosed by Criteria of Katz and of Goldberger*

Case No.	RV (mm.)	LV (mm.)	Heart Weight (Gm.)	% Heart Wt. above Normal	Goldberger's Criteria	Katz's Criteria
3	4	15	320	12	Prolonged Q-T	
4	4	16	340	4		$CF_2(V_2)$
5	4	16	350	3		Type I
6	2	16	400	36		Type II

TABLE 12.—*Incidence of Positive Results, Based on Per Cent of Heart Weight above Expected Maximum Normal*

% in Excess of Max. Normal	No. Cases	Gubner & Ungerleider	Sokolow and Lyon	Schach et al.	Goldberger	Katz	Wilson et al.	Noti et al
0–25	32	5	19	6	8	12	26	7
26–50	22	5	17	3	3	8	17	6
51–75	17	4	16	4	7	9	13	4
76–100	8	3	7	4	2	3	8	2
Over 100	4	2	4	1	1	3	4	3

Incidence of Positive Results Based on Percentage of Heart Weight above Expected Maximum Normal

We employed Zeek's criteria[15] for normal heart weight which is based upon body length; only those cases which exceeded the standard deviation above the mean were used in this study.

We analyzed our cases from the standpoint of accuracy of the various authors' criteria when compared with the percentage of heart weight above the maximum expected normal. As seen in table 12, Sokolow's and Wilson's criteria gave the greatest accuracy for all heart weights.

REMARKS

This study tested only the positivity of the various authors' criteria in cases of proved pure left ventricular hypertrophy. It did not test the specificity of these criteria, that is, the occurrence of false positives. In order to do that, these same criteria should be applied to the electrocardiograms in a series of cases with hearts of normal size proved at autopsy.

The various authors' criteria depend on one or more of the following features: (a) RS-T segment or T-wave abnormalities (67 per cent); (b) prolonged Q-T (48 per cent); (c) high voltage (29 per cent); (d) delayed onset of the intrinsicoid deflection or prolonged duration of the QRS (28 per cent); (e) ratios derived from these findings (57 per cent).

Summary and Conclusions

1. The current electrocardiographic criteria for the diagnosis of left ventricular hypertrophy have been subjected to analysis in 100 cases of pure left ventricular hypertrophy proved at autopsy.

2. The criteria of Sokolow, Wilson, Goldberger, and Katz are, in order, the most accurate in the electrocardiographic diagnosis of left ventricular hypertrophy.

3. Using the criteria of Sokolow and/or Wilson, we were able to diagnose correctly 92 of the 100 cases; three in addition were diagnosed by Katz's criteria, and one by Goldberger's criteria giving a total of 96 per cent accuracy in proved cases of left ventricular hypertrophy.

4. Digitalis obscures the diagnosis in many instances where criteria based only upon RS-T segment and T-wave changes are used.

5. A significant association was found between increasing heart weight and increasing accuracy of diagnosis, using Sokolow's criteria.

6. The cases missed by the application of the criteria of Sokolow and Wilson had only minimal left ventricular hypertrophy.

Summario e Conclusiones in Interlingua

1. Le criterios electrocardiographic traditional pro le diagnose de hypertrophia sinistroventricular esseva analysate in 100 casos de pur hypertrophia sinistroventricular confirmate per medios autoptic.

2. Le criterios de Sokolow, Wilson, Goldberger, e Katz es in iste ordine le plus exacte criterios in le diagnose electrocardiographic de hypertrophia sinistroventricular.

3. Per medio del criterios de Sokolow e/o Wilson nos succedeva a diagnosticar correctemente 92 del 100 casos. In plus tres casos esseva diagnosticate secundo le criterios de Katz; un altere secundo illos de Goldberger. Assi le total del exactitude diagnostic in demonstrate casos de hypertrophia sinistroventricular ascendeva a 96 pro cento.

4. Digitalis obscura le diagnose in multe casos si le criterios usate es limitate a illos basate super cambiamentos del segmento RS-T e del unda T.

5. Esseva constatate un significative correlation inter augmentate pesos cardiac e augmentate exactitudes diagnostic secundo le criterios de Sokolow.

6. Le casos non identificate per le criterios de Sokolow e Wilson habeva hypertrophia sinistroventricular solmente in grados minimal.

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An Analysis of Activation in Human Atria

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The P wave and PsÊ-loop were derived from coplanar outlines of the contour of seven human atria, including left atrial enlargement, in which it was assumed that the process of depolarization spread in a radial fashion from the sinoatrial node. The "derived" planar projections of the P waves of the standard leads and PsÊ-loops were similar in relative amplitude and general contour to those recorded electrocardiographically and vectorcardiographically prior to death.

SINCE an organized conduction system has not been demonstrated in the atria and because of the thinness of atrial muscle, the excitation wave is usually considered to spread through these structures in a simple radial fashion. Such an order of activation is less complex than that occurring in the thicker ventricles with their intricate conduction system and may, therefore, be susceptible to simpler methods of analysis. If a radial spread of activation is considered to occur and if certain assumptions regarding the anatomy of the atria are made, an approximate analysis of the electrocardiographic and vectorcardiographic manifestations of atrial excitation becomes feasible.

Methods and Materials

In the analysis to be presented, the atria were considered as two surfaces. One of these consisted of those portions of the free walls of the atria which were visible on the external surface of the heart (free external atrial walls). The remainder of the atria, which included the interatrial septum and those portions of the free walls which were not visible on the external surface of the heart (free internal atrial walls), were considered to form the second surface.

Activation was assumed to begin on the free external atrial wall at the anterior margin of the junction of the superior vena cava and the free external wall of the right atrium. This point represents the approximate location of the superior portion or head of the sinoatrial node as described by Keith and Flack.[1] It was further assumed that the wave spread in all directions at uniform speed. This assumption is supported by the studies of Lewis[2] and those of Puech and coworkers.[3] The latter group interpret their data to indicate that, with the exception of the taenia terminalis region, conduction speed in dog atria was virtually constant. Since the atria were divided into two sections for this analysis, it was necessary to locate the point of origin of the impulse relative to each of these sections as illustrated diagrammatically in figure 1. Figure 1*A* represents the unopened atria with the point of origin of the activation wave shown at SF. From this point, impulses were considered to pass radially into the free wall of the right atrium spreading parallel with endocardial and epicardial surfaces and simultaneously over the superior portions of that atrium into the interatrial septum. To locate the point of impulse formation relative to the interatrial septum, the section of atrium containing that point was considered to be unfolded into the plane of the interatrial septum as shown in figure 1*B*. In this figure, point S represents the site of impulse formation in relation to the interatrial septum. Since the distance which the activation wave must travel from the point of origin to some portions of the left atrium is shorter via the septum than through the free atrial walls, the point S was also located in relation to the external wall of the left atrium as shown in figure 1*C*. In this figure the free external atrial walls have been "unfolded" onto a plane surface and the septum has been divided to show the apparent location (S) of the site of origin of impulses which pass into the free wall of the left atrium from the septum. The point F represents the site of origin of impulses which pass directly into the free wall of the right atrium.

The atrial outlines used in this study were obtained by dissecting human atria in the following fashion. The unopened atria were filled with cotton introduced through the atrioventricular valves from the opened ventricular cavities. The approximate portions of the free external walls which faced anteriorly, laterally and posteriorly with the heart approximately in the anatomic position were determined. A rough outline of the margins of the intact atria in their approximate anatomic position was obtained by wrapping a strip of tracing paper around the atria and tracing their outline. Vertical

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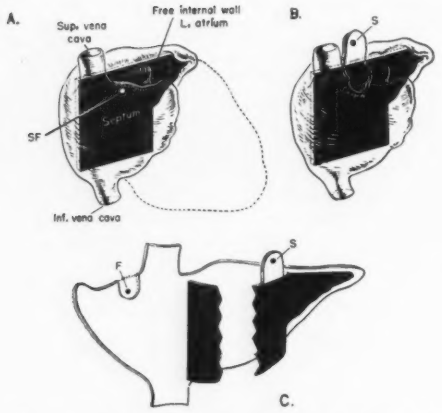

FIG. 1. The relations of the pacemaker in the sino-atrial node are diagrammatically illustrated. *A* shows the unopened atria with the pacemaker represented by the point SF. The septum and the internal surface of the free wall of the left atrium are shown in black. The internal surface of the free wall of the right atrium is not shown. *B* shows a section of free right atrial wall containing the pacemaker (S) unfolded into the plane of the septum. *C* shows a coplanar outline of the external surface of the free atrial walls with the pacemaker shown at F and at S.

lines dividing anterior, lateral and posterior portions were drawn through this outline on the unfolded tracing paper. Although for convenience of analysis the points S and F are shown (fig. 1*C*) as widely separated sites of impulse origin, in the intact atrium they are in fact the same point. The anterior and posterior sections were considered to lie parallel to the frontal plane of the body and the lateral sections to be perpendicular to this plane or parallel to a sagittal plane through the body. The entire thickness of the free external atrial walls was reflected from other portions of the atria in two separate segments illustrated in figure 2. They were then completely removed by cutting at their line of junction with the septum. These two segments which represented the major portion of the free atrial walls were then properly oriented in the plane and within the rough outline of their contour obtained on the tracing paper. The septum and free internal walls were then made coplanar and their outline was traced. Although the spatial orientation of the interatrial septum and the free internal atrial walls was complex, it was considered in the specimens studied that the major portion of the septum was perpendicular and the free internal atrial walls were parallel to the frontal plane of the body. A vertical line dividing the septum and free internal atrial walls was drawn on the outline of this surface (fig. 3*C*).

The division of the atria into sections parallel with the frontal plane and with the sagittal plane is illustrated in figure 3. Figure 3*A* shows a coplanar outline of the unrolled free external atrial walls and its division into anterior, posterior and lateral portions, and 3*B* shows the spatial orientation these portions of the atria were considered to have in this study. Figure 3C shows the coplanar outline of the septum and the free internal atrial walls, and figure 3*D* shows the spatial orientation these portions were assumed to have.

The spread of the activation wave was represented on the unfolded surfaces described as a series of concentric arcs drawn about the site of impulse formation. Since the site of impulse formation was represented by two points in relation to the free external atrial walls a set of arcs was drawn about each of these points.

In each of the sections described, the length of the chord of an arc defined by the limits of the section depicting a given moment in the excitation process was taken as the magnitude of an electric vector acting at that moment. This vector was assigned a direction perpendicular to the chord

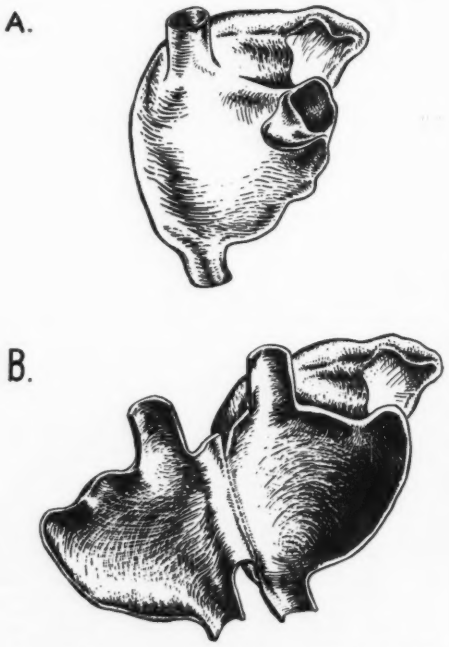

FIG. 2. The removal of the free external wall of the right atrium from other portions of the atria is illustrated. *A* shows the dissection beginning at the right atrial appendage. In *B* the free external wall of the right atrium is shown attached only to the atrial septum. The free external wall of the left atrium was removed in a similar manner leaving the interatrial septum and free internal atrial walls.

under consideration. By this means a series of vectors from each of the sections representing portions of the atria was obtained. When arcs drawn about both points S and F appeared in a single section of the atria, the respective chords were then defined by the limit of the section and the point of intersection of the arcs, and two vectors were given magnitudes equal to those of the chords and directions perpendicular to them. The vectors obtained from that section of the atria located posteriorly were then added to any occurring simultaneously in the portions of the atria located anteriorly. These resultant vectors were given a common origin and their termini joined in their proper time sequence to give a figure analagous to the frontal plane projection of the PsÊ-loop. In all operations in which vectors from two or more sections of the atria were added or given a common origin, the resultant vectors were oriented as they would have been in the unopened atria. (See figures 2 and 3.)

All vectors derived from those portions of the atria which were considered to lie parallel to the sagittal plane were given a common origin, and those which occurred simultaneously were added vectorially. The termini of the resultant vectors were then joined in their proper time sequence to give a figure representing the sagittal plane projection of the PsÊ-loop.

The analysis is illustrated in figure 4. Figure 4*A* shows the outline of the unrolled free external walls of the atria of a normal heart and 4*B* shows the septum and the free internal atrial walls. The

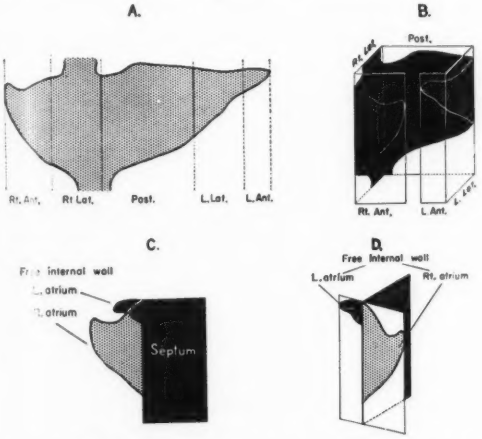

FIG. 3. Division of the atria into sections parallel with the frontal and sagittal planes is illustrated. The coplanar outline of the free external walls of a normal specimen is shown in *A*, and its assumed orientation is shown in *B*. The septum and free internal walls are shown in *C*, and their assumed spatial orientation in *D*.

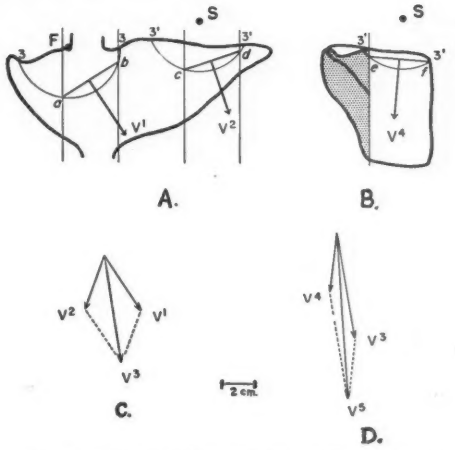

FIG. 4. The method of analysis employed in these studies is illustrated. The coplanar outline of the free external atrial walls of a normal specimen is shown in *A*, and the coplanar outline of the septum and free internal atrial walls is shown in *B*. The derivation of a vector in the sagittal plane for the stage in the activation process represented by the arcs labeled 3 and 3′ indicating portions of the wave front is illustrated. Vector V^1 has been made equal in length to the chord ab and given a direction perpendicular to that chord. Vector V^2 has been made equal in length to the chord cd and perpendicular to that chord. In *C*, vectors V^1 and V^2 have been added to give vector V^3. Vector V^4 has been made equal in length to the chord ef and directed perpendicular to that chord. In *D*, vectors V^3 and V^4 are added to give V^5 which is the effect in the left sagittal plane of activation at the stage represented by the arcs labeled 3 and 3′.

site of impulse formation is represented by points F and S. As discussed, both F and S represent a single site of impulse formation, but F shows this site in its normal relation to the free wall of the right atrium while S represents the apparent point of origin of impulses which entered the free atrial walls from the septum. The atria have been divided into portions parallel to the frontal and sagittal planes (figs. 4*A* and *B*).

In figures 4*A* and 4*B*, a series of concentric arcs about the points representing the site of impulse formation are shown. Each of the arcs about a single point represents the activation process at a given moment. The arcs were numbered consecutively; those which occurred simultaneously were designated by the same number, and those associated with B were primed. The derivation of vectors from two simultaneous arcs (numbers 3 and 3′) in the lateral portions of the atria is illustrated. The vector V^1 was assigned a magnitude equal to the length of the chord CD and a direction perpendicular to that chord. Similarly, vector V^2

was assigned a magnitude equal to the length of the chord EF and a direction perpendicular to that chord. Vectors V^1 and V^2 were then oriented as they would have been in the unopened atria and added vectorially to give V^3 as shown in figure 4*C*. A simultaneous vector, V^4, was derived from arc number 3′ as it appeared on the interatrial septum. Vectors V^3 and V^4 were added vectorially to give vector V^5 which was the resultant in the sagittal plane of that stage in the activation process represented by arcs 3 and 3′. The vector representing the manifestation in the frontal plane of activation at this moment was obtained by carrying out a similar procedure using those portions of the same arcs which were within the anterior and posterior sections of the atria.

When this procedure was carried out with concentric arcs placed 1 cm. apart, a series of vectors representing the effect of activation in the frontal and sagittal planes at several sequential intervals was obtained. Joining the termini of these vectors in their proper time sequence gave figures analogous to the frontal and sagittal plane projections of the PsÊ-loop.

P waves were derived from the loops in the conventional fashion for comparison with those actually recorded in the standard leads. The time scale was arbitrarily chosen to conform to average normal P-wave time–amplitude relationships.

Seven human atria were employed in this analysis. Two of the specimens were atria of normal size, two were from patients with rheumatic disease of the mitral valve and had left atrial enlargement, and three showed right atrial enlargement, two resulting from cor pulmonale and one from congenital pulmonary stenosis. Electrocardiograms showing a normal sinus mechanism were available on all subjects making it possible to compare the form of the P waves recorded electrocardiographically with those constructed as outlined. The spatial vectorcardiogram of one patient recorded with the equilateral tetrahedron reference system was available for comparison with the frontal and sagittal plane projections of the constructed PsÊ-loop.

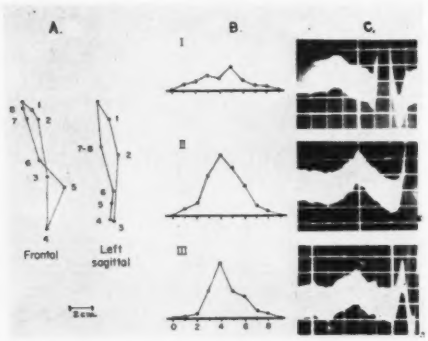

FIG. 5. *A* shows the frontal and sagittal plane projections of the PsÊ-loops derived from the normal atrial specimen shown in figure 4. The derived P waves are shown in *B*, and the P waves of the electrocardiogram recorded before the patient's death are shown in *C*.

RESULTS

Normal Atria. In the two normal atrial specimens analyzed, the relative amplitudes of the derived P waves were similar to those of the P waves in the standard leads of the electrocardiogram recorded before the patient's death. The general contour of the derived waves was remarkably similar to that of the recorded P waves although some differences in form were present (fig. 5).

Recorded PsÊ-loops of these patients were not available for comparison with the derived projections; however, the configuration and orientation of the derived loops were similar to normal PsÊ-loops recorded in this laboratory.

The coplanar outline of one normal atrial specimen was shown in figure 4. Figure 5*A* shows the frontal and left sagittal plane projections of the PsÊ-loop derived from this specimen. The derived P waves are shown in figure 5*B*, and the electrocardiographically recorded P waves are shown in figure 5*C*. The general form and the relative amplitudes of the derived waves may be seen to be similar to those in the recorded electrocardiogram.

Left Atrial Enlargement. In the two specimens with left atrial enlargement studied, the relative amplitudes and general contour of the derived waves were similar to those of the P waves in the electrocardiogram recorded prior to the patient's death. Both the derived waves and the electrocardiographically recorded P waves had a longer duration than those of the subjects with atria of normal size. In each instance the notched wave which is usually associated with left atrial enlargement occurred in both the derived and the actual P waves in lead I.

Since the characteristics of the PsÊ-loop in left atrial enlargement are not established, comparison with actual recorded loops could not be made. The frontal plane projections of the two derived PsÊ-loops were located in the

fth and sixth sextants of a triaxial reference ystem. The left sagittal plane projection of ne was located in the fifth and sixth sextants hile the other was confined to the fifth sextant f a triaxial reference system applied to that lane with the ±180 degree axis located anteriorly. Both frontal plane projections and one agittal plane projection had figure-eight configurations, while the left sagittal plane projection of the other was a simple loop inscribed in a clockwise direction. Characteristic of both frontal plane projections was a rapid movement of the loop to the right and then to the left resulting in a notching of the derived wave in lead I.

The coplanar outline of one of the specimens showing left atrial enlargement is shown in figure 6*A*. Figure 6*B* shows the frontal and left sagittal plane projections of the PsÊ-loop derived from this specimen. The derived P waves are shown in figure 6*C*, and the electrocardiogram recorded prior to the patient's death is shown in figure 6*D*. The general form and relative amplitudes of the derived and recorded P waves are similar.

Right Atrial Enlargement. Three atrial specimens showing enlargement of the right atrium were studied. When right atrial enlargement was present, a greater amount of atrial musculature was found to lie parallel to the frontal plane than in the atria of normal size and those with left atrial enlargement. In the method employed in this study the increased amount of muscle so located resulted in vector forces of increased magnitude in the frontal plane. This in turn was reflected in the derived P waves as increased amplitude in one or more leads. Such increased amplitude of the P waves is consistent with the clinical observation of high peaked P waves in the presence of right atrial enlargement. As was true of the normal atria, and those showing left atrial enlargement, the general contour and the relative amplitudes of the derived waves were similar to those of the P waves in the electrocardiograms recorded prior to death. Both the derived and recorded waves of the three subjects studied were high and peaked and of greatest amplitude in lead II.

The frontal plane projections of the three

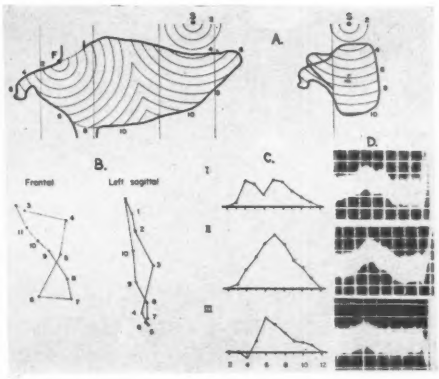

FIG. 6. The coplanar outline of a specimen showing left atrial enlargement is shown in *A*. The scale of this and the following illustration is indicated by the concentric arcs which were placed 1 cm. apart. The frontal and sagittal projections of the PsÊ-loops derived from this specimen are shown in *B*, and the derived P waves and the P waves in the electrocardiogram are shown in *C* and *D*.

derived PsÊ-loops were located in the fifth and sixth sextants of the triaxial reference system. Two of the sagittal plane projections were located entirely within the fifth sextant, while one was within the fifth and sixth sextants of a triaxial reference system applied to that plane. All frontal plane projections were inscribed in a clockwise direction, with two of the records so inscribed that the line crossed itself near the distal tip of the loop. Two of the sagittal plane projections were inscribed in a clockwise direction, and one formed a figure-eight.

The coplanar outline of a specimen showing massive enlargement of the right atrium is shown in figure 7*A*, and the frontal and left sagittal plane projections of the PsÊ-loop derived from this specimen are shown in figure 7*B*. The frontal and left sagittal plane projections of the spatial vectorcardiogram recorded prior to this patient's death with the equilateral tetrahedral reference system are shown in figure 7*C*. The orientation, general form and direction of inscription of the derived projections of the PsÊ-loop were similar to those of the PsÊ-loop actually recorded. The P waves derived for the standard leads are shown in figure 7*D*, and the P waves recorded simul-

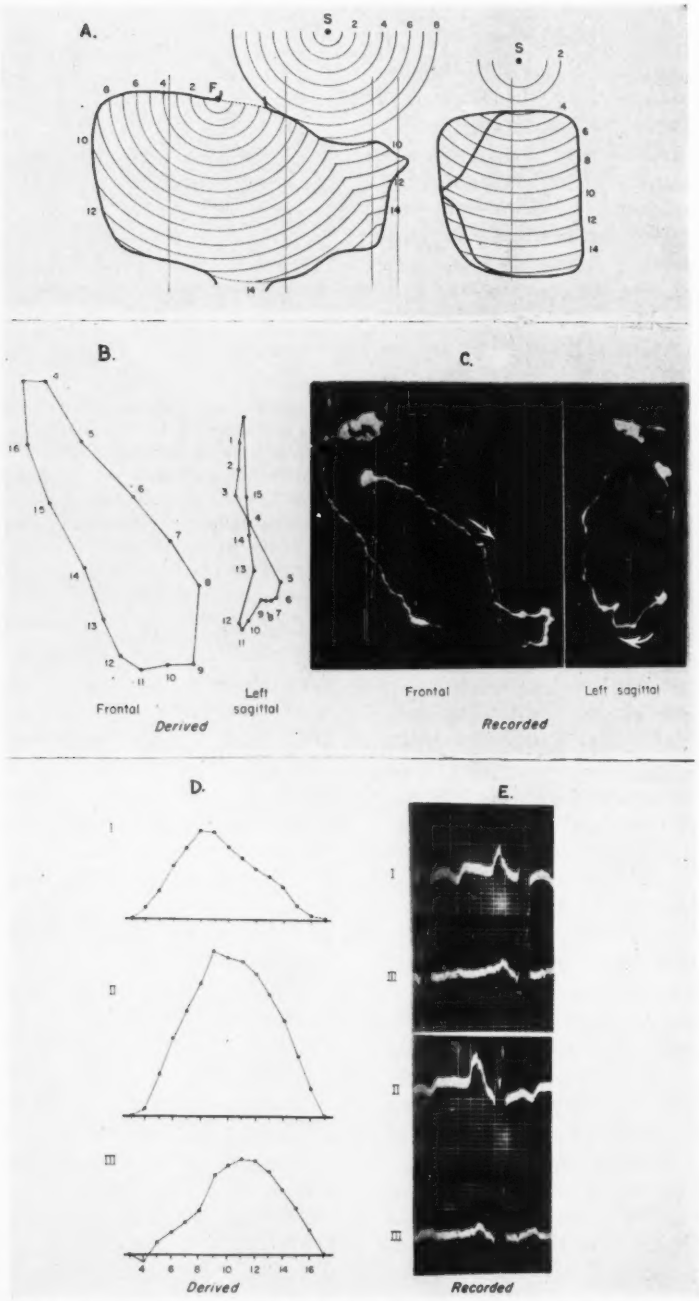

FIG. 7. The coplanar outline of a specimen showing massive enlargement of the right atrium is shown in *A*. Frontal and sagittal projections of the PsÊ-loops derived from this specimen are shown in *B*, and these projections of the PsÊ-loop recorded with the equilateral tetrahedron reference system are shown in *C*. P waves plotted from the frontal plane projections of the derived PsÊ-loops are shown in *D*, and the P waves recorded in simultaneous pairs are shown in *E*.

taneously in pairs prior to the patient's death are shown in figure 7*E*. The general form and relative amplitudes of the derived waves may be seen to be similar to those of the recorded P waves. It may also be noted that the peak of the P wave in lead III of both the recorded electrocardiogram and the derived waves occurs later than the peak in leads I and II. The temporal relationships of various portions of the derived P waves agree remarkably well with those of the recorded P waves.

Discussion

Because of the limited state of knowledge several assumptions which are known to be only partially correct have been made in this analysis to facilitate the calculations. For example, the treatment of the atria as plane surfaces is an oversimplification. The free walls of the atria visible on the external surface of the heart are actually more nearly oriented in the form of a crescent with no sharp boundaries between anterior, lateral and posterior surfaces. Likewise, the orientation of the septum is more complex and more variable than has been assumed in this study. Thus some portions of the atria which were considered to influence only the form of the frontal plane projection also contribute to the form of the sagittal plane projection of the PsÊ-loop, and some portions which were considered to influence only the sagittal plane projection influence also the form of the frontal plane projection. Furthermore the superior and inferior surfaces of the atria have not been considered in this study. Another source of error was the failure to take into account all the physiologic openings in the atria.

Simultaneous depolarization and repolarization in the atria may have further limited this analysis. MacLeod's observations[4] indicated that repolarization in the frog atria began before depolarization was completed and this may be true for man as well. Modifications of the method reported would be suitable for studies relevant to this problem. It was not possible to assess the importance of the errors introduced by the simplifying assumptions employed in these studies.

The excitation wave was considered to spread through the atria in a uniform radial fashion from the site of impulse formation. This order of excitation is supported by the studies of Lewis[5] and of Prinzmetal and co-workers.[6] The observations of Eyster and Meek,[7] however, led them to conclude that even though no specialized conducting tissues exist in the atria, impulses spread preferentially over certain paths to reach the atrioventricular node. The recent studies of Puech and associates[3] on auricular activation in the dog's heart although showing a virtually constant conduction speed in the right atrial body and appendage found it always higher in the region of the taenia terminalis. Results of the present study appear to support the view that activation of the atria proceeded in a regular radial fashion, since the form of the derived PsÊ-loops and P waves closely resembled those actually recorded. It is possible, however, that preferential conduction paths to the A-V node operated without significant influence on the form of the PsÊ-loop and P waves while the bulk of the atrial musculature was activated in a radial fashion.

In this analysis the site of impulse formation was assumed to lie at the anterior margin of the junction of the superior vena cava and the right atrium. This point corresponds to the superior portion of the collection of sinoatrial nodal tissue originally described by Keith and Flack[1] and represents the approximate locus which Lewis[2] and others[3, 7] concluded was the pacemaker of the normal heart. Since the form and orientation of the PsÊ-loops and the form of the P waves derived in this study were dependent on the site of impulse formation, these results tend to support the view that impulses originated in the head of the sinoatrial node.

In spite of the limitations, the analysis presented appears to have value in understanding the form of normal and abnormal PsÊ-loops and P waves. In each instance the derived P waves were similar in contour and in relative amplitude to those actually recorded before the subject's death, and in the case of the one subject whose spatial vectorcardiogram was available the PsÊ-loop was similar to that which was calculated. In general, the derived P waves had a more complex form than was

apparent in the P waves of the electrocardiogram. This, however, may have been at least partially due to the lack of detail in the P wave recorded electrocardiographically. Studies reported by Langner,[8] in which the cathode ray oscilloscope with an expanded time scale and amplifiers with high frequency response were used, demonstrated details in the configuration of the P wave which were not apparent in those recorded with the conventional electrocardiograph.

The analysis outlined accounted for some of the differences in normal P waves and PsÊ-loops and those occurring with atrial enlargement. Right atrial enlargement resulted in frontal plane vectors obtained by the method outlined which were of greater magnitude than those derived from normal atria. This was a consequence of the greater mass of atrial musculature located anteriorly which produced high peaked P waves in some of the standard leads of the electrocardiogram. The duration of the derived P waves in atrial enlargement was longer than in normal atria. These characteristics of form and duration are consistent with those observed in the electrocardiograms of patients with right atrial enlargement. The form and the orientation of the atria in which the left atrium was enlarged gave rise to calculated PsÊ-loops of increased duration and of such a form that prominent notching of the derived P waves in one of the standard leads was present. Such P waves are known to occur commonly with left atrial enlargement.

Summary

1. Seven human atria were dissected in a manner which allowed a coplanar outline of their contour to be made. By assuming that the normal site of impulse formation was located at the head of the sinoatrial node and that the activation wave spread in a simple radial fashion from this point, it was possible to obtain "derived" planar projections of the PsÊ-loops and standard lead P waves.

2. The derived P waves were found to be similar in relative amplitudes and general contour to those recorded electrocardiographically prior to death. A spatial vectorcardiogram of one patient recorded prior to death was also similar in general form, orientation and direction of inscription to the PsÊ-loop derived from the atrial outline.

3. Left atrial enlargement resulted in derived P waves of greater duration than those derived from normal atria. Rapid changes in the direction of inscription of the frontal plane projections of the derived PsÊ-loops were associated with notching of the derived P waves in lead I. These characteristics of the derived PsÊ-loops and P waves were clearly the result of the size, contour and orientation of the atria.

4. Enlargement of the right atrium resulted in a greater mass of atrial musculature oriented parallel to the frontal plane. This produced vectors of increased magnitude in the frontal plane projection of the "derived" PsÊ-loops and was reflected by high, peaked derived P waves in the standard leads.

Summario in Interlingua

1. Septe atrios human esseva dissecate de maniera a permitter le execution de un delineation coplanar de lor contorno. Per supponer que le sito normal del formation del impulso se trova al capite del nodo sino-atrial e que le unda de activation se expande radialmente ab iste puncto, nos poteva obtener "derivate" projectiones planar del spiras PsÊ e del unda P in derivationes standard.

2. Le derivate undas P se monstrava simile in amplitude relative e contorno general al undas P registrate ante le morte. Un vectocardiogramma spatial registrate ante le morte in le caso de un del patientes esseva etiam simile in forma general, orientation e direction de description al spira PsÊ derivate ab le contorno atrial.

3. Allargamentos sinistroatrial resultava in durationes del derivate unda P plus extendite que in le caso de atrios normal. Rapide cambiamentos in le direction del inscription de projectiones in le plano frontal de derivate spiras PsÊ esseva associate con indentationes in le derivate unda P del derivation I. Iste characteristicas del derivate spiras PsÊ e del undas P esseva clarmente le resultato del dimensiones, del contorno, e del orientation del atrios.

4. Allargamentos del atrio dextere resultava
ı un augmento del massa de musculatura
trial que esseva orientate parallelmente al
lano frontal. Isto produceva vectores de aug-
ıentate magnitude in le projection in le plano
ontal de "derivate" spiras PsÊ e esseva re-
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The Effect of Hexamethonium upon Cerebral Blood Flow and Metabolism in Patients with Premalignant and Malignant Hypertension

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In 13 patients with grade III or grade IV hypertensive retinopathy the effect of intramuscular hexamethonium bromide on cerebral circulation and metabolism has been studied. The results have been compared with Dewar's study of hexamethonium in less severe hypertensive patients and with Kety's results following differential spinal sympathetic block. Sixty minutes after intramuscular hexamethonium, mean arterial blood pressure fell 39 per cent, cerebral vascular resistance was reduced 29 per cent, and cerebral blood flow decreased 16 per cent. Cerebral oxygen consumption was maintained at the expense of a reduction in cerebral venous oxygen saturation.

THE EFFECT of hexamethonium upon blood flow in various organs of hypertensive patients has been reported by several investigators. Cardiac output was reduced in compensated patients.[1] Renal blood flow decreased initially but returned to control value despite a continued reduction in arterial blood pressure.[1, 2] Blood flow through the abdominal viscera decreased in proportion to the fall in arterial blood pressure.[3] The present report concerns the effect of hexamethonium upon cerebral hemodynamics and metabolism in 13 patients with severe hypertension.

METHOD

Thirteen hospitalized patients with premalignant or malignant hypertension were studied in the supine position. Ages ranged from 28 to 48 years. Six patients exhibited grade III and seven grade IV hypertensive retinopathy (Keith-Wagener-Barker). Mild to moderate impairment of the renal function was demonstrated by standard clinical tests, but blood nonprotein nitrogen value was within the normal range. In four of the patients a cerebral vascular hemorrhage had occurred six months to one year prior to the present study. Cardiac functional capacity was I–II. None of the group had previously received hexamethonium.

Control measurements were made, and hexamethonium was administered intramuscularly (mean average dose 1.0 mg. per kilogram). Mean arterial blood pressure fell within 5 to 30 minutes. The second blood flow determination was made 60 minutes after drug injection, at which time the blood pressure had stabilized. Cerebral blood flow (CBF) was determined by the nitrous oxide method of Kety and Schmidt.[4] Mean arterial blood pressure (MABP) was obtained directly by a needle in the femoral artery attached to a Statham strain gage or damped mercury manometer. Blood gas analyses for oxygen, carbon dioxide, and nitrous oxide were made with the Van Slyke-Neill manometric apparatus. Venous oxygen saturation was determined by

$$\frac{\textit{Venous oxygen content.}}{\textit{Hemoglobin} \times 1.34}$$

Cerebral oxygen consumption ($CMRO_2$) and cerebrovascular resistance (CVR) were calculated as previously described.[4]

RESULTS

The results are presented in tables 1 and 2. Mean arterial blood pressure fell from 181 to 111 mm. Hg, representing a decrease of 39 per cent. Cerebral vascular resistance was reduced 29 per cent. Cerebral blood flow fell from 55 to 46 cc. per 100 Gm. per minute (16 per cent). These changes were significant

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Dr. Rowe is a Research Fellow of the American Heart Association.

TABLE 1.—*The Effects of Hexamethonium in Malignant hypertension. Blood Pressure and Blood Constituents*

Pt.	Sex	Age	Fundi	Dose (mg.)	Wt. (Kg.)	Side Effects	Femoral MABP mm. Hg		Cardiac Rate Per min.		CO_2 Content Vol. %				O_2 Content Vol. %				O_2 Sat. %	
											Art.		IJV		Art.		IJV		IJV	
							C	D	C	D	C	D	C	D	C	D	C	D	C	D
A.M.	M	36	III	50	61		189	149	78	100	33.2	34.6	38.8	39.6	16.6	16.2	10.2	9.5	58.3	56.1
E.J.	F	28	III	56	46		147	128	73	96	46.8	48.0	51.6	53.6	14.6	14.3	9.0	8.3	54.7	53.2
O.K.	F	48	IV	100	85	Nausea	195	141	82	88	46.4	43.6	51.5	52.3	18.0	18.1	11.1	9.6	58.4	51.2
D.S.	F	41	III	75	65		195	92	84	72	41.4	44.2	49.1	53.3	17.9	16.6	10.7	6.9	59.4	40.4
M.S.	F	35	III	50	65	Nausea, Emesis	179	92	82	120	44.3	47.1	52.7	54.6	19.5	17.8	10.0	8.1	55.5	50.1
W.M.	M	41	IV	40	59		159	143	74	88	55.2	57.7	60.4	62.4	15.5	14.9	10.2	9.4	65.8	62.6
C.K.	F	40	IV	100	82	Pallor, Nausea	189	126	72	88	40.7	39.2	47.0	46.5	17.3	16.3	10.8	8.5	56.8	47.7
G.H.	M	43	IV	80	55	Nausea	175	107	110	85	49.3	49.5	57.0	58.2	18.9	18.9	11.8	10.1	54.6	49.5
F.C.	F	36	III	37.5	45	Nausea	176	100	80	100	51.3	49.4	56.8	57.6	17.9	17.5	12.2	8.8	64.9	51.1
A.K.	F	42	IV	85	60	Pallor	205	135	95	90	51.0	51.2	56.9	59.4	18.5	17.3	12.2	9.6	66.0	55.2
T.J.	M	28	IV	25(I.V.)	60	Nausea	188	90	100	110	28.9	29.1	35.7	38.9	16.5	16.0	9.3	6.9	56.3	41.4
E.S.	M	41	IV	63	74	Weakness	172	70	88	85	58.3	59.2	61.6	64.1	11.3	10.4	7.4	5.6	56.0	46.7
R.M.	M	40	III	50	69	Weakness	186	69	100	84	42.6	43.0	52.4	56.3	20.7	19.4	10.4	6.1	46.4	28.0
Mean of all observations							181	111*	86	93	45.3	45.8	51.7	53.6*	17.2	16.4*	10.4	8.3*	57.9	48.7*

* Signifies a statistically significant change ($p < 0.01$).
C = control; D = after hexamethonium; Art. = arterial blood; IJV = internal jugular venous blood.

($p < 0.01$). Cerebral oxygen consumption did not change significantly in spite of the reduced blood flow through the brain. This was maintained at the expense of a reduction in cerebral venous oxygen saturation. Such a reduction indicates a decrease in the ability of the cerebral circulation to meet the metabolic needs of the brain. Partial compensation did occur due to the decrease in cerebral vascular resistance. This is demonstrated in figure 1. The horizontal line indicates no change in cerebral venous oxygen saturation. The open circles represent the actual reduction in

TABLE 2.—*The Effects of Hexamethonium in Malignant Hypertension. Cerebral Circulation and Metabolism*

Patient	CBF cc./100 Gm./min.		A-IJVo_2† Vol. %		CMRo_2 cc./100 Gm./min.		CVR mm. Hg / cc./100 Gm./min.	
	C	D	C	D	C	D	C	D
A.M.	49	53	6.4	6.7	3.1	3.6	3.9	2.8
E.J.	74	69	5.6	6.0	4.1	4.1	2.0	1.9
O.K.	42	34	6.9	8.5	2.9	2.9	4.6	4.1
D.S.	46	38	7.2	9.7	3.3	3.7	4.2	2.4
M.S.	46	40	9.5	8.7	4.3	3.5	3.9	2.3
W.M.	77	69	5.3	5.3	4.1	3.7	2.1	2.1
C.K.	52	41	6.5	7.8	3.4	3.2	3.6	3.1
G.H.	46	36	7.1	8.8	3.3	3.2	3.8	3.0
F.C.	58	42	5.7	8.7	3.3	3.7	3.0	2.4
A.K.	55	48	6.3	7.7	3.5	3.7	3.7	2.8
T.J.	53	31	7.2	9.1	3.8	2.8	3.6	2.9
E.S.	62	54	3.9	4.8	2.4	2.6	2.8	1.3
R.M.	51	39	10.3	13.3	5.3	5.2	3.6	1.8
Mean..	55	46*	6.8	8.1*	3.6	3.5	3.5	2.5*

C = control; D = after hexamethonium.
* Signifies a statistically significant change ($p < 0.01$).
† A-IJVo_2 = cerebral oxygen extraction.

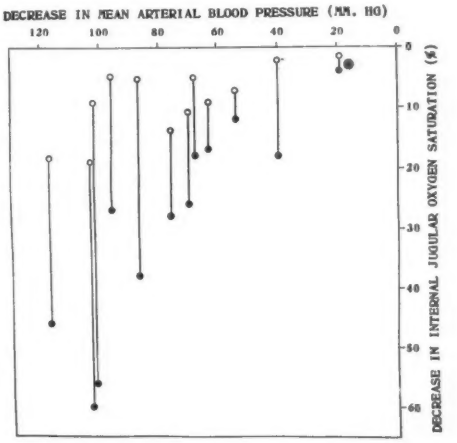

FIG. 1. Decrease in internal jugular oxygen saturation plotted against decrease in mean arterial pressure following hexamethonium. The horizontal line at zero represents no change in cerebral venous oxygen saturation. Open circles represent the actual reduction in oxygen saturation of internal jugular venous blood for each patient following hexamethonium. Solid circles denote values calculated on the basis of no change in cerebrovascular resistance.

cerebral venous oxygen saturation for each patient following hexamethonium. The solid circles denote values calculated on the basis of no change in cerebrovascular resistance. There was not a sufficient number of values to justify calculating a statistical curve of regression, but the figure suggests that a majority of our patients exhibited a progressive decrease in cerebral venous oxygen saturation as the mean arterial blood pressure fell. However the change in cerebral venous oxygen saturation was not as severe as would have occurred without a significant cerebrovascular relaxation.

Other significant metabolic changes included a decrease in arterial oxygen content and a rise in cerebral venous carbon dioxide content following hexamethonium.

Discussion

Cerebral blood flow and cerebral oxygen consumption were observed to be within the normal range in 13 patients with premalignant or malignant hypertension. There was a marked and consistent increase in cerebrovascular resistance averaging 119 per cent, which appeared to be roughly correlated with the grade of retinopathy.

These studies indicate that the reduction in cerebral vascular resistance, although significant, was not sufficient to compensate completely for the fall in blood pressure following hexamethonium. Some information regarding the possible mechanism of the reduction in cerebrovascular resistance in hypertensive patients following hexamethonium may be obtained by comparing our results and those of Dewar[5] with those of Kety[6] following differential spinal block. Kety observed a 16 per cent reduction in cerebral vascular resistance following a decrease in blood pressure brought about by a procedure which acted on vascular beds remote from the brain. We observed a 29 per cent and Dewar a 28 per cent reduction in cerebrovascular resistance following parenteral hexamethonium. The blood pressure reductions reported by Kety and by Dewar were of comparable magnitude, while that observed by us was of greater severity. In each of these studies the arterial blood pressure was lowered to approximately the same level. It would then appear that hexamethonium is more effective than differential spinal block in reducing resistance to blood flow through the brain in hypertensive patients. This could be the result of (1) blocking of the autonomic innervation of the cerebral blood vessels, (2) a more profound change in cerebral metabolites, and (3) a direct action on the smooth muscle of the cerebral vessels. Most of the experimental evidence indicates that the cerebral sympathetics play a minor role in the regulation of cerebral vascular resistance in hypertensive patients which would tend to discredit the first possibility. Since the changes in cerebral venous oxygen and carbon dioxide were comparable in both the differential spinal block and our hexamethonium studies, this would hardly account for the difference observed in the cerebral vascular resistance. It seems, therefore, that the most likely explanation is a direct action of hexamethonium on cerebral blood vessels.

Dewar observed essentially no change in cerebral blood flow following hexamethonium in six hypertensive patients. Five of his patients had grade II and one had grade IV hypertensive retinopathy. Administration of hexamethonium resulted in a reduction in mean arterial blood pressure from 153 to 107 mm. Hg (30 per cent). All of the patients in our series had either grade III or grade IV hypertensive retinopathy. Following hexamethonium there was a 39 per cent reduction in mean arterial blood pressure and a 16 per cent decrease in cerebral blood flow. In both studies the cerebral vascular resistance was reduced by approximately 30 per cent. Therefore, in our patients the cerebral blood vessels were incapable of relaxing to a degree sufficient to maintain normal cerebral blood flow in contrast to Dewar's observations. It seems likely that the severity of the hypertensive vascular disease could account for the reduction in cerebral blood flow. These studies seem to indicate that the mean arterial blood pressure should not be acutely reduced with hexamethonium by more than 30 per cent of the control value in patients with premalignant or malignant hypertensive vascular disease.

Morris[8] reported a 39 per cent reduction in mean arterial blood pressure in normotensive

patients following hexamethonium infusion. He observed a 30 per cent decrease in cerebral blood flow compared with our 16 per cent change from the control value. However in his patients the cerebral arterial perfusion pressure following hexamethonium was 62 mm. Hg. This degree of hypotension probably accounts for the differences in our results. The slight increase in blood volume, due predominantly to an increase in plasma volume observed by Morris following hexamethonium, might play a role in lowering the arterial oxygen content.

Summary

1. The effect of hexamethonium bromide upon cerebral hemodynamics and metabolism was studied in 13 patients with severe hypertension.

2. Sixty minutes after intramuscular hexamethonium mean arterial blood pressure fell 39 per cent, cerebral vascular resistance was reduced 29 per cent, and cerebral blood flow decreased 16 per cent.

3. Cerebral oxygen consumption was maintained at the expense of a reduction in cerebral venous oxygen saturation.

4. The possible mechanisms of action of hexamethonium upon the cerebral vascular bed are discussed.

5. These studies, in conjunction with the observations of Dewar, seem to indicate that the mean arterial blood pressure should not be acutely reduced with hexamethonium by more than 30 per cent of the control value in patients with either premalignant or malignant hypertensive vascular disease.

Summario in Interlingua

1. Le effecto de bromido de hexamethonium super le hemodynamica e metabolismo cerebral esseva studiate in 13 patientes con sever hypertension.

2. Sexanta minutas post le administration intramuscular de hexamethonium le valores median del pression arterial cadeva per 39 pro cento; le resistentia vascular in le cerebro esseva reducite per 29 pro cento; e le fluxo sanguinee in le cerebro suffreva un reduction de 16 pro cento.

3. Le consumption cerebral de oxygeno esseva mantenite al costo de un reduction del saturation cerebro-venal de oxygeno.

4. Le possibile mechanismo del action de hexamethonium super le base vascular del cerebro es discutite.

5. Iste studios—conjunctemente con le observationes de Dewar—pare indicar que in patientes con morbo vascular hypertensive in phases premaligne o maligne le valores median del pression arterial non deberea esser reducite acutemente per plus que 30 pro cento del valores de controlo.

Acknowledgments

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Patterns of Surface Temperature Response to Various Agents

By Lothar Wertheimer, M.D., Walter Redisch, M.D., Kurt Hirschhorn, M.D., and J. Murray Steele, M.D.

Surface temperature response to 15 agents was studied at 20 C. and 55 per cent humidity. Toe temperature was considered representative of the body's "glomus area." Temperatures at forehead and cheek represented the "blush area." Diethylaminoethanol, Hydergine, tetraethylammonium chloride, Priscoline, hexamethonium, Ilidar and Dibenzyline produced a prompt rise in temperature in the glomus area without affecting the temperature in the blush area; nicotinic acid, Roniacol, histamine and papaverine caused the opposite response. Nitroglycerin had no effect on the temperature in the blush area; with the subject recumbent, it caused a fall in the glomus area. Hypertonic saline, aminophylline and Banthine had no effect on either glomus or blush areas.

DURING the course of studying effects of various "vasodilator" agents on surface temperature and peripheral blood flow, it appeared that the types of response elicited differed from one another. It was decided, therefore, to study systematically the vascular response to agents belonging to several distinct pharmacologic groups.

This report deals with response of surface temperature to various agents under controlled environmental conditions where the behavior of surface temperatures can be predicted with some accuracy.[1-4] Since it was desired to test vasodilators, an environment calling forth a mild vasoconstrictor response was used, namely a temperature of 20 C. and humidity of 55 per cent. Under these circumstances, the following adjustments normally take place:

1. Within 30 to 60 minutes the temperature of the toes decreases until it approaches closely environmental temperature; it then remains relatively constant.

2. The temperature measured at the finger tips usually continues to fluctuate markedly, and its pattern of behavior varies from subject to subject.

3. The temperature of the rest of body surface (forehead, cheek, xiphoid process of sternum, thigh and leg) remains relatively constant throughout the experiments (34 to 35 C. on forehead and cheeks, and about 3 to 6 C. lower at test places over the rest of the body, roughly according to the downward gradient described in the literature).[5-7]

The difference in behavior of the toes as compared with the fingers suggests that the lower extremities are concerned with the coarse basic adjustment to environment, while the upper extremities provide for the fine minute-to-minute regulation[1-7] and response to such varying impulses as may arise from a full bladder, increased digestive or peristaltic activity, or mental and emotional stimuli.

The constancy of the temperatures of the forehead and cheek, which contain no glomi but possess the faculty of visible blushing, is in striking contrast to the variability of the temperature of the toes and fingers, which are known to be very rich in the neuromuscular-vascular thermostats called glomi.[8, 9] For the purpose of grouping the surface temperature responses to pharmacologic agents, the terms "glomus area" and "blush area" will be used in this paper. Since the fingers did not yield a constant baseline in response to the mild vasoconstrictor stimulus of 20 C., and since such

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TABLE 1.—*Surface Temperature Responses to Fifteen Agents*

Agent	Physiologic-Pharmacologic Classification of Agent	Dose Employed	No. of Subjects	Av. Change in Glomus Area (baseline temp. 20–21 C.)	Average Change in Blush Area (baseline temp. 34–35 C.)
Nitroglycerin	"Coronary" vasodilator and "peripheral" vasodilator	0.6 mg. sublingually	recumbent 7 erect 3	−1.8 C. 0	0 0
5% Saline	Hypertonic solution	250 ml. i.v.	4	0	0
Aminophylline	Bronchodilator, diuretic	225 mg. i.v.	4	0	0
Banthine	Cholinergic blocker	50 mg. i.m.	2	0	0
Papaverine	Antispasmodic alkaloid	100 mg. i.v.	2	0	+1.3 C.
Histamine	Capillary vasodilator	0.025 mg. i.v.	2	0	+1 C.
Nicotinic acid	"Peripheral" vasodilator	100 mg. i.v.	5	0	+2.4 C.
Roniacol	"Peripheral" vasodilator	100 mg. i.v.	8	0	+1.8 C.
Diethylaminoethanol	Vasodilating component of procaine	4.3 Gm. i.v.	7	+4.1 C.	0
Hydergine	Central vasomotor depressor	0.3 mg. i.v.	3	+5.0 C.	0
Tetraethylammonium chloride	Sympathetic ganglionic blocker	300 mg. i.v.	3	+4.0 C.	0
Priscoline	Sympatholytic	50 mg. i.v.	4	+4.5 C.	0
Hexamethonium	Sympathetic and parasympathetic ganglionic blocker	10 mg. i.v.	4	+5.6 C.	0
Ilidar	Adrenergic blocker	3 mg. i.v.	3	+4.7 C.	0
Dibenzyline	Adrenergic blocker	120 mg. orally O.D. for 5 weeks	13	+4.5 C.	0

baseline appears essential for measuring responses to a vasodilator stimulus[10] the toes were chosen as representative of the "glomus area"; forehead and cheek were used as representative of the "blush area."

METHOD AND MATERIAL

The subject, under basal conditions, was placed in the constant-temperature room maintained at 2[illegible] C. and 55 per cent humidity. Surface temperature was recorded on a Speedomax from both great toes, the forehead and the cheek. The drugs were not administered until temperatures had remained constant for at least 30 minutes.

The response to 15 agents was tested in 74 experiments. Fourteen of these agents were administered in single doses: one of them was given in intravenous infusion, one sublingually, one by intramuscular route and 11 by intravenous injection. The fifteenth agent was fed orally over a four-week period and experiments were repeated at regular intervals in a manner previously described.[11]

RESULTS

Seven of the drugs used had a marked dilator effect upon the glomus area and did *not* affect the blush area (fig. 1). These drugs included: diethylamino alcohol, three blockers of sympathetic pathways,[12, 13, 14] (tetraethylammonium chloride, Priscoline and hexamethonium), an agent known to depress central vasomotor tone (Hydergine),[15] and two so-called adrenergic blockers (Dibenzyline and Ilidar) known to interfere with the activity of circulating

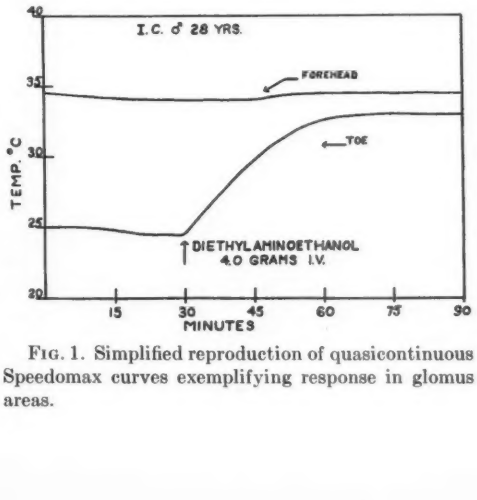

FIG. 1. Simplified reproduction of quasicontinuous Speedomax curves exemplifying response in glomus areas.

sympathomimetic amines[11, 16] (table 1). All of these agents in acute experiments produced a prompt rise in the temperature of the toes. Their effect was about equal in degree (toe temperature rose from about 20 C. to between 24 and 25 C.), and it invariably outlasted the experiment (about 45 to 60 minutes after onset of response). These facts suggest that the action of the drugs in this group is probably mediated by a rather sudden decrease of sympathetic vasomotor tone. The mode of action of diethylaminoethanol is entirely unknown, but, since its effect on surface temperature so closely resembles that of the six other drugs, all of which are known to affect sympathetic vasomotor tone in one way or the other, the inclusion of alcohol in this group seems justified.

Four of the agents tested have regularly increased the temperature in the blush area, and not in the glomus area (fig. 2). The resulting rise in temperature in the blush area was as prompt as that described in glomus area, but the rise was smaller (from about 35 C. to about 37 C.) and of much shorter duration (15 minutes in the average). (See table 1.) Nicotinic acid and Roniacol are closely related chemically but have no chemical or pharmacologic relationship to histamine and papaverine.

Vasodilator action produced upon surface vessels by the four agents in the blush area is confined to the minute circulation since there are no glomi in this area. Their mode of action is unknown. It has been suggested[17] that cholinergic sympathetic fibers might be dominant in maintaining vasomotor tone in the blush area of the face in contrast to other surface areas where adrenergic fibers are assumed to be the main pathways of vasoconstrictor impulses.[18] In order to obtain some information concerning this question, Banthine[19] was injected intramuscularly in doses of 50 mg. It produced regularly the signs of cholinergic blockade, especially marked dryness of the mouth and transient disturbance in visual accommodation, but no measurable effect on surface temperature (table 1). Thus, while blocking of adrenergic sympathetic innervation in various ways regularly increased the toe temperature and never affected the temperature of the blush area, cholinergic blockade produced no effect in either of the tested areas.

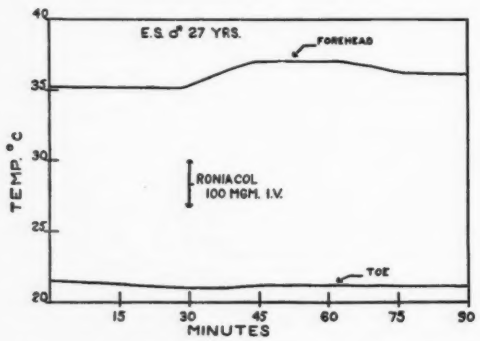

FIG. 2. Simplified reproduction of quasicontinuous Speedomax curves exemplifying response in blush areas.

Hypertonic saline and aminophylline likewise had no measurable effect on surface temperature in either blush or glomus areas (table 1).

Nitroglycerin was given in both the erect and the recumbent positions since it had been found[20, 21] that administration of nitroglycerin with the subject in the erect position may induce circulatory collapse by postarteriolar dilatation, venous pooling and reflex arteriolar constriction but that its administration with the subject in the recumbent position will not produce this response. There was a slight decrease in toe temperature following nitroglycerin when the subject remained recumbent; no measurable change occurred in either test area when the subject was tilted into a semierect position to an angle of 65 degrees and the drug was then administered (table 1). It should be noted that tilting from the recumbent to the erect position, per se, produced a decrease in toe temperature comparable to that produced by nitroglycerin when administered to the recumbent subject.

DISCUSSION

It has been shown[22] that one and the same vasomotor agent or procedure may produce vasodilatation in one vascular bed and simultaneously vasoconstriction in another. The data presented here indicate that even within one vascular bed (in this case that of the skin)

areas can be differentiated by specific patterns of vasomotor response. Thus, although various drugs may be grouped together under the general designation vasodilator or vasoconstrictor, their individual effects may vary widely according to the location, extent and mechanism of action. Detailed information concerning the action of each drug thus adds to the knowledge of the physiologic behavior of the vascular system. Likewise, such information is obviously essential for choosing the most suitable drug for a particular therapeutic purpose.

Summary and Conclusions

1. Surface temperature response of normal subjects to 15 agents reported to have vasodilator action was tested in an environment of 20 C. and 55 per cent humidity (mild vasoconstrictor stimulus).

2. Four agents tested regularly caused a temperature rise in the blush area and none in the glomus area, and seven produced a marked temperature rise in the glomus area but not in the blush area. Four agents tested produced no increase of skin temperature in either of the test areas.

3. The seven agents which affected the temperature of the glomus area all act by interfering with the transmission of adrenergic impulses at various levels of sympathetic vasomotor pathways.

4. Interference with the transmission of postganglionic cholinergic impulses (by the administration of Banthine) did not result in any measurable temperature changes in the areas tested.

Summario in Interlingua

15 agentes con un reputation de virtute vasodilatative esseva studiate in lor effectos super le temperatura superficial. Le genas e le fronte esseva usate como representantes del areas erubescente, le digitos del pede como representantes del areas glomeral. In un ambiente de calor moderate (20C con 55 pro cento de humiditate) le sequente resultatos esseva obtenite: Papaverina, histamina, acido nicotinic, Roniacol resultava invariabilemente in augmentos de temperatura del areas erubescente sed nunquam del areas glomeral. Per contrasto, diethylaminoethanol, Hydergina, chlorido de tetraethylammonio, Priscolina, hexamethonium, Ilidar, e Dibenzylina augmentava invariabilemente le temperatura del areas glomeral sed non afficeva le temperatura del areas erubescente.

Blocages cholinergic per medio de Banthina, aminophyllina, e solution salin hypertonic non resultava in ulle effecto super le temperatura del pelle. Nitroglycerina produceva un abassamento del temperatura in le areas glomeral quando le subjecto se trovava in un position recumbente.

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Unrecognized Hyponatremia and Hypochloremia

By GEORGE C. GRIFFITH, M.D. AND OSCAR MAGIDSON, M.D.
With comments by: EUGENE A. STEAD, JR., M.D. AND LOUIS LEITER, M.D.

DR. GRIFFITH: "To reduce edema, to decrease, insofar as possible, the sodium content of the body": From the time the role of sodium in the retention of fluid was first established, this has been a cardinal prescription in the management of congestive heart failure and other conditions in which there is an extracellular accumulation of fluid. This precept is rooted in the belief that fluid in the peripheral tissues superimposes an added burden upon an already handicapped heart and should, therefore, be removed as speedily as possible, by whatever means or combination of means are at hand.

The mistaken belief that congestive failure can exist only in the presence of excessive sodium retention, coupled with the conviction that salt restriction is not in itself harmful, has led to abuses of a regimen that, judiciously employed, is invaluable in the treatment of heart failure. Years ago, before we learned to remove salt from the diet efficiently, before the time of powerful mercurial diuretics, and before the development of ion-exchange resins, hyponatremia and hypochloremia were observed on but few occasions. The methods then in use were too crude to reduce levels of sodium and chlorides in the body to a dangerous level. But today our tools are more precise, and constant safeguards are necessary.

In each of the cases to be presented, the patient was from the first under the care of experienced and able physicians; yet, in each instance, symptoms of electrolyte depletion were overlooked until such time as the salt depletion syndrome had become irreversible and death was inevitable. Since Dr. Magidson is well acquainted with the cases to be discussed, I shall ask him to present the salient facts in each case and aid in the discussion. Dr. Magidson, will you please present the first case.

DR. MAGIDSON: The patient, a 51-year-old female, first was seen in November, 1952, at which time she complained of orthopnea, shortness of breath and palpitation on slightest exertion, easy fatigability, complete nervous exhaustion, and stiffness of the hands and feet. Swelling of the abdomen, legs and back had been present for about a week. The purpose of the consultation was to determine whether heart surgery would be beneficial.

History: Although cyanosis in early infancy suggested the presence of a congenital heart lesion, the patient was apparently in good health until her thirty seventh year, when she suffered a severe episode of pneumonia. Digitalis was prescribed at that time, and had been continued to the date of the examination. The patient's gall bladder was removed in her forty fourth year. At 48, she underwent thyroidectomy, which resulted in an episode of profound shock. Although the thyroidectomy apparently had been of decided benefit, episodes of heart failure requiring recurrent hospitalization dated from that operation and necessitating discontinuance of her employment as a typist-clerk. At the time of her examination, she had just returned from the hospital.

In addition to digitoxin, the patient was taking mercaptomerin every third day. She reportedly drank but one cup of coffee a day, plus a little ginger ale and 7-Up; she had been drinking distilled water for a week. She used no tobacco or alcohol.

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Physical examination: The patient, who spoke slowly as if under a sedative, was pale and icteric, with dry skin and dry hair. Veins in her neck were distended, pulsating freely, even when the patient was sitting upright. Pulse rate was rapid and the rhythm totally irregular. Blood pressure was 120/80. On percussion, the lungs showed dullness below the angle of the scapula. Many fine, moist rales were audible throughout both lung fields.

The heart was enormously enlarged, the point of maximum impulse occurring in the third and fourth left intercostal spaces, 3 cm. to the left of the midline. The apex beat was located in the sixth intercostal space at the midaxillary line. Rhythm was totally irregular (auricular fibrillation). The aortic first and second sounds could be heard clearly, and the pulmonic second sound was accentuated many times over the aortic. A grade II systolic murmur was audible in the tricuspid area, and a moderately soft grade II apical systolic murmur could be heard in the left midaxillary line. Venous pressure was markedly increased (estimated as 160 mm. water, minimum). The liver could be palpated 10 cm. below the costal margin. The abdomen contained free fluid. Pitting edema was present over the sacrum, and thighs and legs showed marked swelling.

Fluoroscope: The lung fields were very cloudy. The heart was greatly enlarged, with the enlargement most marked in the region of the right ventricle. The pulmonary arteries and veins were markedly prominent. No enlargement of the left atrium was observed.

Electrocardiogram: Right ventricular hypertrophy pattern and uncontrolled auricular fibrillation were reported.

Clinical diagnoses: 1. Congenital interatrial septal defect, 2. Cardiac enlargement (+70 per cent), 3. Auricular fibrillation, uncontrolled, and 4. Marked right and left congestive heart failure. 5. Class IV E.

Dr. Griffith suggested that the patient might be a candidate for closure of the septal defect after she had been thoroughly "dried out" and compensated, provided the defect would be confirmed by cardiac catheterization. He recommended that the patient be placed on a low sodium diet, and that digitalis be increased to a point where the ventricular rate would remain in the seventies.

The patient was admitted to the Los Angeles County Hospital on November 11, 1952, for a stay of nine days. During this time she was maintained on a low sodium diet (approximately 300 mg.) but received no mercurials. Her condition improved considerably under this regimen, and she was discharged from the hospital with the proviso that she remain on the low sodium diet and reenter the hospital at a later date for cardiac catheterization.

On November 30, 1952, the patient reentered the hospital and was again found to be in increasing congestive failure, in spite of the low sodium diet she had been following at home. The low sodium diet was continued during the 14 days of this hospitalization and, on four occasions, the patient was given intramuscular injections of 2 cc. of meralluride sodium solution (Mercuhydrin sodium solution) with good diuretic response. The patient was discharged on Dec. 12, 1952, after cardiac catheterization, with instructions to continue the low sodium diet.

The patient's condition was diagnosed as rheumatic heart disease in the cardiac conference held on December 22. The low sodium diet was continued in an effort to clear the congestive failure. By Jan. 12, 1953, gross failure was no longer apparent, but the patient was instructed to continue the low sodium diet at home.

On Jan. 19, 1953, the patient was rehospitalized because of increasing dyspnea and orthopnea, which had been noted for three days. Signs of severe cardiac failure were present. Again, the patient was maintained on a low sodium diet, and 2 cc. Mercuhydrin was administered without response although water intake was adequate. On January 23, the patient became confused and lethargic. Lethargy continued and deepened until, on January 26; the patient responded only to painful stimuli.

Blood chemistry was reported for the first time on January 26. Non-protein nitrogen was 27 mg. per 100 cc.; serum carbon dioxide, 33 mEq. per liter; serum chlorides, 59 mEq. per liter; serum sodium, 109 mEq. per liter; and serum potassium, 2.6 mEq. per liter. Urine output was only 550 ml. on this day.

Presence of the salt depletion syndrome was first suspected at this time, and 1000 cc. of 3 per cent solution of sodium chloride with 1 Gm. of potassium chloride added was administered intravenously. Later the same day, 500 cc. of a 5 per cent glucose solution containing 0.5 Gm. potassium chloride was administered. The following day, an additional 1000 cc. of the sodium chloride solution with 2 Gm. of potassium chloride was administered. The patient expired on Jan. 28, 1953.

This case encompasses most of the features usually present in instances where the salt depletion syndrome has escaped detection: 1. The patient suffered from edema of cardiac origin but was apparently free from renal pathology and was, therefore, an appropriate candidate for dehydration therapy. 2. Dehydration therapy had worked for a time for this patient, but had broken down. 3. Breakdown was ascribed not to the salt-depletion syn-

dome, but to the need for more vigorous methods for promotion of diuresis. 4. Mercurials were used to increase diuresis, forcing increased salt leakage.

By the time electrolyte depletion is suspected, the condition has often become irreversible and terminates in death. In view of the very low level recorded, potassium depletion may have been a factor in this patient's death.

DR. GRIFFITH: The maintenance of this patient on a low sodium diet for over three months without the safeguard of frequent blood chemistry studies and other laboratory determinations is insupportable. Yet, because clinicians are often unaware of the importance of maintaining serum sodium and chlorides at levels sufficient to permit relatively unimpaired renal function, they often neglect to request laboratory determinations, or purposely omit these in order to spare the patients "needless expense."

I should like to call your attention to the period of increasing dyspnea and orthopnea in this patient, which followed a period of satisfactory diuresis, during which interval the patient was free from gross signs of cardiac failure. Reappearance of symptoms of cardiac failure erroneously was interpreted as a sign that more vigorous diuretic measures were needed, and the low sodium diet was supplemented by administration of mercurials. Recurrence of edema in the patient should have put the physician on notice that serum sodium and chloride levels had dropped to dangerously low levels. Sudden increase in body weight by water retention after a period of successful diuresis should always be suspect, particularly if accompanied by an increase in serum nonprotein nitrogen or a rise in blood urea nitrogen, indication either that urinary volume is not sufficient to carry away the nonprotein nitrogen or that renal disease is present. In either case, dehydration therapy should have been terminated at once.

Clinical signs and symptoms should have suggested the probability of salt depletion. In spite of the excess fluid in their peripheral tissues, patients suffering from salt depletion complain of thirst, but they experience dryness of the throat which makes swallowing difficult. They show signs of lassitude, apathy, weakness and anorexia. They vomit, or complain of muscular cramps. In cases of extreme salt depletion, patients often become disoriented and even psychotic.

As persons on low sodium diets are often receiving digitalis, the salt depletion syndrome is occasionally mistaken for a toxic reaction to the digitalis. Measurement of plasma sodium and chloride levels sometimes will distinguish between the two conditions; however, the two conditions may coexist. If potassium depletion also is present, response to digitalis may be intensified.

Once the condition has been recognized, correction is best accomplished by oral administration of salt or, if vomiting precludes oral salt administration, through intravenous salt administration. Since infusion of an isotonic solution would not raise sodium and chloride levels of the body fluids sufficiently unless very large amounts were administered—a hazardous procedure in the patient with congestive failure—a hypertonic solution is used. A 3 or 5 per cent concentration of sodium chloride, administered slowly, is usually satisfactory; its administration causes no significant or constant elevation of venous pressure. Unless the condition has persisted for such a time that it has become irreversible and death is imminent, as in the cases here presented, clinical improvement parallels closely the restoration of electrolyte balance.

Potassium is administered to these patients for two purposes: (1) to restore potassium levels; and (2) because alkalosis is refractory to sodium chloride therapy if potassium deficiency continues. Infusions of saline or glucose without the addition of potassium would increase the potassium loss, as the kidneys preferentially excrete potassium rather than sodium. Dr. Magidson, will you please present the next case.

DR. MAGIDSON: This patient, a 39-year-old male formerly employed as a carpenter, was transferred to the Los Angeles County Hospital on May 9, 1950, from a nearby private hospital, where he had been under treatment for heart disease and subacute bacterial endocarditis for a period of seven weeks. The state

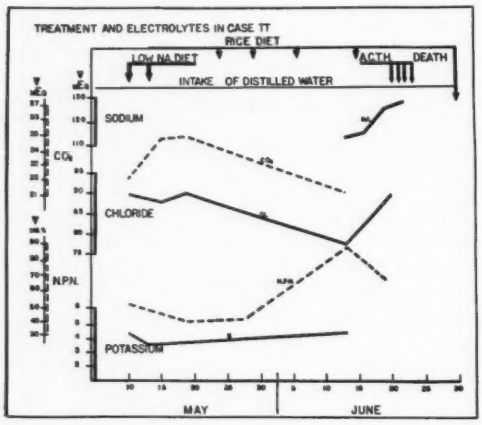

FIG. 1

of the electrolytes and the treatment are shown graphically in figure 1.

History: The patient suffered penile trauma at the age of three, and symptoms of penile obstruction were noted in his early 'teens. Otherwise, he is alleged to have been in good health until April, 1949, when he was hospitalized for a week because of the development of jaundice, ascites and edema of the ankles. Three months later, the patient consulted a urologist because of pyuria observed since discharge from the hospital. Retrograde studies disclosed a urethral stricture, which subsequently was dilated satisfactorily. In October, 1949, the patient was hospitalized because of a urinary tract infection for a 30 day period. On admission, his temperature registered 104 F. During a short hospital stay in January, 1950, the patient's condition was diagnosed as heart disease with ascites and edema of the ankles, accompanied by subacute bacterial endocarditis. A recurrence of subacute bacterial endocarditis in April, 1950, resulted in the seven-week period of hospitalization which was referred to at the opening of this case history, after which he was transferred to the Los Angeles County Hospital.

Physical examination: Upon admission, the patient was noted to be dyspneic and ascitic, with marked edema of the legs. Blood pressure was 145/40 mm. Hg. Pulse rate was 80; respiratory rate, 20. Crepitant rales were heard over both lung bases. The heart was moderately enlarged, with sinus rhythm. Evidence of free aortic incompetence was noted. The abdomen was moderately distended from ascites. The liver was not felt to be enlarged. Four plus pitting edema of the legs and abdominal wall was present. Venous pressure was estimated to be 300 mm. of water. Using Decholin, the arm to tongue circulation time was found to be 30 seconds.

Laboratory: Hemoglobin was 17.9 Gm. per 100 cc.; white blood cells, 14,800, of which 86 per cent were polymorphonuclear leukocytes. A trace of albumin was present in the urine, together with numerous pus cells and red blood cells.

Two days following his admission to the Los Angeles County Hospital, the patient was reported to be "paranoid and psychotic." He was put on a low sodium diet, and aminophylline and 2 cc. of Mercuhydrin were administered intravenously. The following day, 3500 ml. of sanguineous fluid was removed from the abdomen by paracentesis, and another 8 cc. aminophylline and 2 cc. Mercuhydrin were administered. On May 13, the patient was started on a rice diet, on which he was maintained for the next 41 days. During this period, he drank 1 to 1.5 liters of distilled water daily. The diuretic effect of the rice diet was reinforced on the fifteenth, seventeenth, nineteenth and twenty fourth day of May by intravenous injections of aminophylline, 10 cc., and Mercuhydrin, 2 cc. On May 30, 600 ml. of sanguineous fluid was removed by paracentesis from the left side of the chest.

The day following hospitalization at the Los Angeles County Hospital, blood chemistry was as follows: serum chlorides (as sodium chloride), 89.6 mEq. per liter; serum potassium, 4.1 mEq. per liter; and nonprotein nitrogen, 48 mg. per 100 cc. Carbon dioxide combining power was 21.8 mEq. per liter. Icterus index was 26 units.

Serum sodium was not measured separately until June 13, at which time it was 112 mEq. per liter. By this date, nonprotein nitrogen had climbed to 91 mg. per 100 cc., and serum chloride values had slipped to 77.2 mEq. per liter. Potassium concentration and carbon dioxide combining power remained unchanged. The patient refused food. Cerebral depression was marked, and hospital attendants commented on the patient's lethargy. A 3 per cent solution of sodium chloride (500 ml.) was administered intravenously, raising sodium and chloride values slightly but resulting in no clinical improvement.

Corticotropin (ACTH), 15 mg., was administered on each of four successive days, starting with June 20. Although the patient seemed slightly more alert on the first day of this medication, his condition deteriorated rapidly, and he became icteric (icteric index had climbed to 58 units on June 22). On June 23, the rice diet was discontinued, and he was returned to a low sodium diet. Death occurred on June 30, 1950.

DR. GRIFFITH: In the case just presented, dangerously low levels of serum sodium and chlorides were ignored, and drastic measures were employed in an attempt to rid the patient of excess extracellular fluid: low sodium diet, the even more severe rice diet for a period of 41 days, and the administration of aminophylline

and mercurial diuretics on six occasions. Sodium and chloride levels were depleted further by abdominal paracentesis on May 12 and thoracic paracentesis on May 30. This case serves to re-emphasize a point I have always made to my students: edema in the peripheral tissues is not a danger to the patient which calls for immediate, heroic measures. The "drying out" process should occupy an extended period, rather than hazard the safety of the patient. If vigorous measures are employed, a close watch should be kept for clinical signs and symptoms of distress, and for laboratory values which indicate that sodium and chloride levels have reached perilously low levels.

DR. MAGIDSON: I should like to raise a question or two about the case just presented. Do we keep a close watch for *perilously low levels of sodium and chloride*, or can we adopt a policy which forestalls this finding? Obviously, the object of vigilance in these cases is to prevent occurrence of these levels. When the patient is on a low sodium intake and has had mercurials, if he fails to respond adequately to mercurials and urine output falls below the fluid intake, and if symptoms begin to occur, we must immediately suspect salt depletion and measure the electrolytes and blood urea nitrogen. I am beginning to feel that failure to take note of a falling urine output in the face of deterioration leads to most trouble.

It is generally acknowledged that low sodium and chloride levels result ultimately in impaired renal function and the events we are discussing. Questions I should like to ask are these: Can electrolyte levels be used to *predict* the events in any one case? How can we assess the flexibility of the kidneys from case to case? In two patients with similarly low electrolytes and similar treatment, one keeps a good urine volume and does well and the other goes into the low salt syndrome. Do you not agree that this may be the case? Another question: Is it the individual with some renal damage who gets into trouble more readily? In the occasional case, may he not manifest a "better" electrolyte pattern than the patient with relatively uninjured kidneys?

DR. GRIFFITH: These are certainly points to be kept in mind and I agree as to their significance. May we have the third case, please, Dr. Magidson.

DR. MAGIDSON: As a third instance of the unsuspected presence of the low salt syndrome, we present the case of a 64-year-old male, in a state of cardiac decompensation from prolonged hypertension, who was already in an irreversible condition of electrolyte depletion on April 19, 1953, when he was admitted to Good Samaritan Hospital with the complaint of shortness of breath, cough, weakness, and swelling of the legs.

History: The patient was apparently well until December of 1951, when he sought medical advice because of ringing in the ears and occasional frontal headaches. Examination at that time revealed an enlarged heart and elevated blood pressure. The physician in attendance advised weight loss and prescribed a diet low in cholesterol.

In August, 1952, shortness of breath again became evident, progressing to orthopnea and accompanied by episodes of acute pulmonary edema. The patient complained of pain in the epigastrium and his legs became swollen. In the next few months, the patient's condition remained stationary; blood pressure averaged 190/130, save for a temporary fall to 120/80 following acute illness. The pulse remained elevated, ranging between 100 and 125, except for a brief period after an acute illness. The heart was observed to be enlarged, with gallop rhythm. A grade II apical systolic murmur was present, and many rales could be heard at the bases of both lungs. A pleural effusion on the right side was drained. Edema of the legs was 2 plus. Treatment included the administration of oxygen and ouabain and rest in bed. The patient was maintained on a low sodium diet and given mercurial diuretics in an effort to clear the failure. Oral medication with hexamethonium drugs in an attempt to maintain blood pressure at a lower level was unsuccessful.

Studies done at an institution in Mexico City revealed elevated nonprotein nitrogen, and blood urea nitrogen of 53 to 63 mg. per 100 cc. One to 2 mg. of blood creatinine was present per 100 cc. A blood Wasserman test was negative. A 24-hour sample of the patient's urine contained 2 Gm. of albumin and many hyalin casts. An electrocardiographic tracing done at this time disclosed an incomplete left bundle branch block, with evidence of left ventricular hypertrophy and suggestion of an old anteroseptal myocardial infarction. Hexamethonium drugs were tried again without success. The patient was considered a poor candidate for sympathectomy.

The patient was brought from Mexico to Los Angeles in the hope that he might be benefited by the lower altitude. The findings, treatment and course follow.

Physical examination: The patient was extremely alert. His color was good. His eyes showed grade II retinopathy. His nose and throat were healthy. Respiratory rate was 32; pulse rate, 110. Blood pressure was 150/120. Many rales were present at the bases of both lungs. His heart showed grade III enlargement with a definite gallop rhythm. A grade II to grade III apical systolic murmur was present. The liver was slightly tender, and could be palpated 8 cm. below the costal margin. The spleen was just palpable. Two plus pitting edema was present. The bladder was empty.

X-ray examination: Marked enlargement of the left ventricle could be observed. A small amount of fluid was present at the bases of both lungs.

Electrocardiogram: Tracing showed a complete left bundle branch block, with probability of an old anteroseptal myocardial infarction.

Laboratory: Blood urea nitrogen was 21 mg. per 100 cc.; blood creatinine, 1.5 mg. per 100 cc.; serum sodium, 119 mEq. per liter; and serum potassium, 5.1 mEq. per liter. Serum chloride determination was not requested.

The day following his admission to the Good Samaritan Hospital, the patient was noted to be cyanotic, and a uremic odor was present on his breath. Weight was 170 pounds, and blood pressure was 160/120 in both arms. Pleural effusion was present on the right side, and rales were audible over the left lung base.

A solution of 5 per cent sodium chloride (500 ml.) was administered intravenously and then a solution containing 5 per cent glucose (500 ml.). Injection of a mercurial diuretic followed. Only a 2 per cent weight loss resulted, therefore administration of additional saline solution preceded further attempts to promote diuresis. Serum sodium concentration was 122 mEq. per liter at this time, and nonprotein nitrogen measured 79 mg. per 100 cc. The following day, the patient's heart tones were good and his lungs were dry. Blood pressure was 140/80 at this time. Additional saline was administered cautiously, but the patient's condition worsened, edema increased and, on May 30, 1953 convulsive twitching was noted. The patient died on the following day.

DR. GRIFFITH: Long-time maintenance on a salt-poor diet in an attempt to reduce hypertension and to clear congestive failure secondary to the hypertension had disturbed the already precarious electrolyte balance in this patient, and he had passed from the therapeutic to the toxic stage of salt-restriction therapy some time before. At the time he was brought to the Good Samaritan Hospital for treatment, the condition was no longer remediable.

COMMENTS

DR. MAGIDSON: The so-called low salt syndrome should be suspected whenever patients who have been maintained on a low sodium diet and/or have responded to mercurial diuretics demonstrate a marked depletion of urinary volume over a period of several days, together with a rapid, progressive gain in weight. Clinical symptoms include thirst which cannot be slaked by water, lethargy, apathy, weakness, drowsiness or restlessness, nausea and mental confusion. The Schales and Schales test for sodium chloride in the urine usually will show little or no precipitate with silver nitrate unless there has been pre-existing renal tubular damage. Anorexia may operate to limit food intake, and vomiting to further depress electrolyte concentration. Decline in plasma chloride values will usually precede fall in plasma sodium concentrations. Elevation of blood urea nitrogen and serum nonprotein nitrogen occurs under these conditions because urinary volume is not adequate to carry away the nonprotein nitrogen.

DR. GRIFFITH: Symptoms of salt depletion result from either sodium depletion, or depletion of serum chlorides; imbalance between the two ions may contribute to acidosis or alkalosis. Under certain conditions, the salt depletion syndrome may occur even if dietary intake of salt is not restricted, i.e., if profuse vomiting occurs, in the presence of excessive diarrhea, if an intestinal fistula is present, or if continuous suction drainage has been established. Any of these conditions results in disproportionate loss of sodium and chloride ions, which may disturb electrolyte balance and initiate the low salt syndrome. Continued loss of gastric juice, for example, will result in hypochloremic alkalosis, which may be accompanied by a rise in the plasma bicarbonate level as a result of the combination of the freed sodium with carbonic acid. On the other hand, continued loss of fluid from the gut distal to the pylorus results in a proportionately greater loss of sodium ions, with resulting acidosis and decrease of plasma bicarbonate. Vomiting or diarrhea during salt restriction therapy will, of course, intensify electrolyte loss. Administration of large amounts of salt free liquid, either orally or

parenterally, also lowers electrolyte concentrations in the body fluids.

Whenever dietary salt is restricted as a therapeutic measure, and whenever conditions exist which operate to derange electrolyte balance within the body, a close check must be kept on electrolyte levels at all times. In addition, levels of nonprotein nitrogen or blood urea nitrogen should be checked for indications of severe dehydration. In hyponatremia blood urea nitrogen may reach 60 to 90 mg. per 100 cc., or even higher.

If salt replacement is indicated, it is important that sodium chloride be given cautiously, in divided doses; in a few cases, the administration of one-third to one-half of the dosage calculated to restore sodium and chloride levels to normal has proved sufficient. The amount of sodium needed is calculated by the following formula:

Patient's weight in kilograms $\times \frac{60}{100} \times$ *(normal mEq − patient's mEq), in which body water is considered to be 60 per cent of body weight.*

Dr. Magidson: I should hate to have this conference on hyponatremia and hypochloremia come to a close without some mention of the abuses of dietary restriction of sodium chloride that occur all too frequently. It is important to remember that dietary restriction of sodium is not justified in every form of heart disease. If the heart disease in the patient is *not associated with sufficient failure to produce renal retention of salt and water*, restriction of the amount of salt in the diet not only is of no value, but may be detrimental to the patient from both psychologic and nutritive standpoints. We have all seen patients who suffer from valvular heart disease unaccompanied by congestive heart failure—rheumatic heart disease or subacute bacterial endocarditis, for example—who have been placed on low sodium diets that are valueless from a physiologic point of view and serve only to focus the patient's attention on his cardiac disability and thus increase his tension and anxiety.

Dr. Griffith: Edema is not invariably due to congestive failure. When edema is present, it is important to determine whether the accumulation of fluid is in fact due to cardiac decompensation or whether it is the result of peripheral venous or lymphatic disease unaccompanied by cardiac decompensation.

Dr. Magidson: It has been our experience that even in the presence of congestive heart failure, diets prescribed are often too low in salt content. Although diets providing 0.5 Gm. of sodium per day or less are justified in the initial treatment of moderately severe to severe congestive failure, the correction of aggravating factors such as hyperthyroidism, inflammatory disease processes or obesity will usually permit some relaxation of dietary salt restriction.

Dr. Griffith: We urge frequent assessment of cardiac status to determine whether heart action has improved to a point where less rigid salt restriction may be observed. Although persons with organic disease who have suffered congestive failure with edema rarely can return to an entirely unrestricted diet, cardiac function may be restored sufficiently that only mild dietary restriction is necessary.

I think we have covered most of the points we wish to make here today. I should like to leave you with a statement I made earlier in this discussion: Edema in the peripheral tissues is not a danger to the patient which calls for immediate removal by drastic, even heroic measures. The "drying out" process should occupy an extended period of time, rather than hazard the safety of the patient and only after adequate rest and digitalization have been evaluated.

Discussion by Eugene A. Stead, Jr., M.D.

Salt restriction never causes harm when congestive heart failure is the central problem, if it is not combined with mercurial diuretics. If one has primarily renal failure, with heart failure being more or less incidental, salt restriction may lead to difficulty.

In many chronic illnesses, low sodium states develop without salt restriction. If the chronic illness is one like congestive failure, or cirrhosis, edema will be present. In brain tumors or malignant hypertension, edema will be absent. These disturbances in electrolyte concentration are in some way related to the severity of illness,

and they will develop in most patients with heart failure if they die slowly. Adding salt to the diet results in an expansion of extracellular fluid volumes with no change in electrolyte concentration but with progressive edema. These conditions are not comparable to salt-losing nephritics as they will not excrete excess amounts of salt on a low salt diet.

Although I agree that the patients reported on were treated without proper laboratory controls, the fact that none of them responded to the administration of salt weakens the argument that they died from salt depletion. As two of the patients were jaundiced, my guess would be that pulmonary infarctions were also important.

I do not agree with the concept that patients who recover from congestive failure are necessarily best treated by liberalizing the salt intake. In many hypertensive patients, keeping the sodium intake below 200 mg. will cause a considerable reduction in blood pressure and a great decrease in heart size. Appreciable reduction in heart size may also occur in the absence of hypertension. A decrease in heart size is of great advantage to the heart mechanically. Adding salt to the diet of a patient with a large heart is undesirable from the cardiovascular side: it is always a compromise to gain other things.

Discussion by Louis Leiter, M.D.

The three cases described illustrate the necessity of differentiating the hyponatremic state due to primary sodium loss or depletion, from the dilution type of hyponatremia which follows excessive retention of water in severe heart failure. The depletion type of hyponatremia should be treated with concentrated salt solution for obvious reasons. The dilution type of hyponatremia in cardiac patients seems to represent excessive antidiuretic hormone activity and abnormal behavior of volume regulating centers in response to increased congestive failure. In this situation the urgent need is not hypertonic saline but improved myocardial function, to promote the excretion of the excess water. This happens without loss of sodium so that the serum level rises by concentration of the extracellular fluid. The daily injection of long-acting Pitressin in patients in controlled heart failure can, by inducing primary water retention and aggravating the congestive state, closely mimic the natural form of dilution hyponatremia. Here, too, addition of sodium chloride is of no therapeutic value. Withholding Pitressin leads to prompt water diuresis and rise in serum sodium level to the control values.

Since the dilution type of hyponatremia is a manifestation of severe heart failure and not of sodium deficiency, its treatment must be directed toward increasing myocardial efficiency, whether by adequate digitalization, restoration of tissue potassium content, control of intercurrent infection, relief of anoxia or other measures. The administration of hypertonic saline solution can be very harmful.

In a given case of hyponatremia, even with extensive laboratory data available, it may be problematic whether the patient is suffering from sodium depletion or sodium dilution, or both. Close clinical observation of the sequence of events may help in this differentiation. Thus, a low serum sodium level in a cardiac patient who has lost weight and mobilized edema rapidly is probably due to depletion. When to this a change in psyche is added and signs of peripheral collapse and gastrointestinal symptoms, the diagnosis becomes quite certain. On the other hand, a low serum sodium in an edematous cardiac who is developing signs of increasing congestive failure and gaining weight, while responding poorly to mercurials, is strongly suggestive of dilution hyponatremia. Careful check of the fluid balance and search for known factors in the aggravation of heart failure will help in the diagnosis. In case of doubt or where the patient presents a mixture of the two syndromes, slow intravenous administration of 5 per cent saline solution in divided doses to elevate the extracellular sodium level by only 5 to 10 mEq. per liter, may significantly improve the condition of a depleted patient and not seriously harm the patient with dilution hyponatremia. Fluid intake must be sharply restricted on the day of the infusion in order to obtain the maximum increase in serum sodium concentration. A

mercurial diuretic should not be administered at this time unless there is pulmonary edema.

Confusion in diagnosis and treatment of a hyponatremic state is compounded by simultaneous hypokalemia and hypochloremic alkalosis, as was likely in case 1. This patient was given a large amount of sodium chloride and very little potassium. In severe heart failure effective digitalization may be impossible without appropriate restoration of tissue potassium depleted by poor intake, mercurial or other diuresis, and emaciation. Attention to potassium deficits may be more important therapeutically than attempts to elevate the serum sodium level. One must consider the physiological balance between these two cations.

Because of the unusual severity of sodium restriction on the Kempner rice diet, no patient should be placed on this regimen without a preliminary determination of the serum electrolyte pattern. In case 2, one may estimate from the sum of serum bicarbonate and chloride concentrations, 111 mEq. per liter, that the serum sodium level was probably as low as 125 mEq. per liter even before paracentesis, the use of the rice diet and mercurials. Under these circumstances, the subsequent downhill course is not surprising. The 250 mEq. of sodium given when the serum sodium level was 112 mEq. per liter would be inadequate in an individual of average weight.

The administration of hypertonic saline in case 3 in an attempt to potentiate mercurial diuresis involves the mistaken notion that a successful diuresis will result in a net negative sodium balance for the period. This is not the case because the increased urinary excretion of sodium never exceeds the amount infused and usually falls far short of it. Often, the patient ends up with more edema than before the infusion because of a limited diuretic response to the mercurial and failure to restrict fluid intake after the administration of hypertonic saline. Although the data available for case 3 are incomplete, it would seem that the patient was retaining water and diluting his extracellular sodium. It is also likely that he was given an excessive amount of hypertonic salt solution for the wrong reasons.

CLINICAL PROGRESS

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Arterial Malformations which Cause Compression of the Trachea or Esophagus

By ROBERT E. GROSS, M.D.

THERE are many vascular malformations in the superior mediastinum which have little or no clinical significance, but some arterial anomalies in this region assume importance because an abnormal or a displaced vessel can compress the trachea or the esophagus (or both) and partly obstruct these vital passages. Since surgical methods are now available for thoracic exploration of even the youngest subjects, it is important to recognize those malformations which threaten health or life; certain of these can now be brought under surgical attack, thus affording relief of the esophageal or tracheal obstruction.

Arterial derangements within the chest are common, can be complex, and can assume many forms. These facts are confirmed by a very extensive literature. A presentation of monographic size would be necessary to list and describe all of the anomalies which have been encountered. It is intended here to deal only with those, which so far have been found at the operating table when attempting to relieve an existing tracheal or esophageal compression. The following sections are based on the study and surgical care of 70 babies and children with such vascular anomalies. Occasionally, one of these vascular malformations might come to light in an adult, but almost certainly the vast majority of malformations, which are serious enough to cause important troubles, will come to the attention of a clinician or a surgeon in the early years of life, as was the experience in the series of cases described here.

The arterial malformations for which surgery has some therapeutic value include *double aortic arch, right aortic arch with a left ligamentum arteriosum, anomalous innominate artery, anomalous left common carotid artery, and aberrant right subclavian artery.*

DOUBLE AORTIC ARCH

Pathologic Anatomy. The fundamental pathologic change is concerned with the fact that the ascending aorta bifurcates into two branches, one passes in front of and to the left of the trachea, while the other progresses to the right of the trachea and esophagus; both limbs then join to form a descending aorta (figs. 1 and 2). In the majority of cases, the left (anterior) arch is the smaller of the two; in a minority, the right (posterior) arch is the smaller in size. The descending aorta is generally on the left side of the spinal column, but in an occasional case it is to the right of the midline (fig. 3). The space between the two aortic arches is insufficient for accommodation of a trachea and esophagus of normal size. Therefore, both of these structures become compressed in the crowded region between the two aortic segments.

Clinical picture. In rare cases, the space provided between the two aortic arch limbs is relatively large; the encircled trachea and esophagus have a fair amount of room and there is little or no attendant difficulty from interference with the functions of these two pathways. However, most subjects with a

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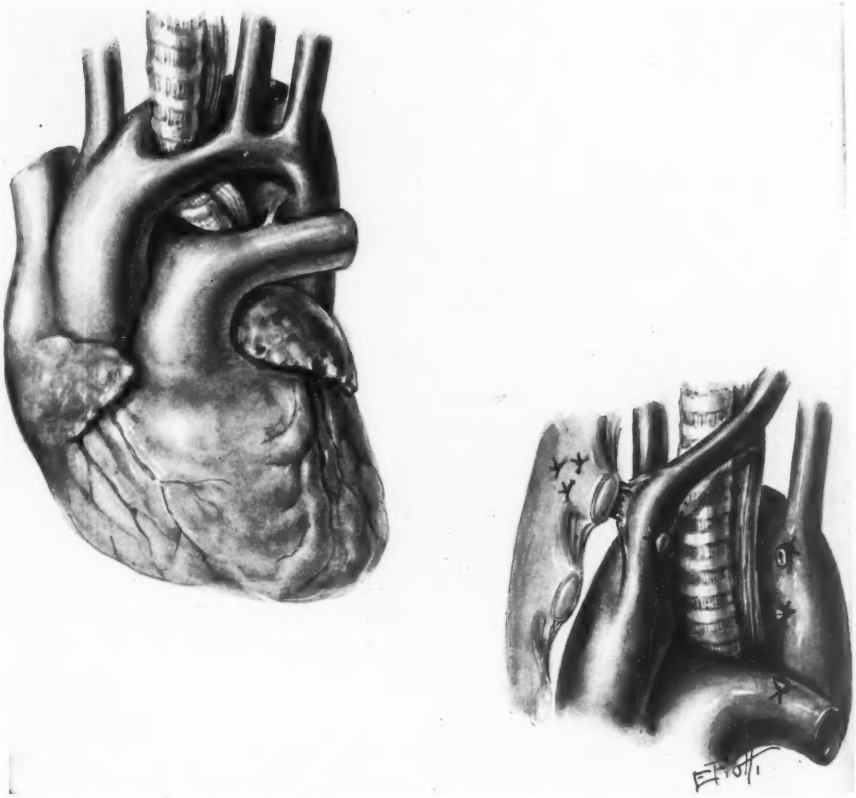

FIG. 1. Double aortic arch producing compression of the trachea and esophagus. *Left.* Preoperative state. There is a small anterior arch and a large posterior limb, which join and form the descending aorta. *Right.* Surgical therapy by dividing the ligamentum arteriosum and also the anterior arch. The left common carotid artery is tacked forward to the sternum, thus keeping it from pressing on the trachea. These various steps give sufficient room for the trachea and the esophagus to bulge to the patient's left and be relieved of constriction.

double aortic arch have very little room between the two arterial limbs, so that the esophagus and particularly, the trachea, are greatly compressed. While a double aortic arch is compatible with a long life and relatively minor symptoms, the anomaly is usually a serious one and has often led to fatality within the first year or two of life; the marked tracheal obstruction has led to superimposed pulmonary infection which has overwhelmed many of these babies.

Most human subjects with a double aortic arch have sufficient symptoms to come to the attention of a physician during infancy. There may be mild or moderate hesitation in swallowing. Of greater significance are the alarming symptoms which come from tracheal narrowing. The respiratory rate is generally increased. The baby struggles to obtain an adequate exchange of air, an effort which often requires the use of the accessory muscles of respiration. During inspiration there may be intercostal and suprasternal retraction. A loud wheeze can be heard by stethoscopic auscultation, but usually the noise is great enough to be heard with the unaided ear many feet or yards away. There is apt to be a "crowing" type of breathing, with a marked inspiratory and expiratory stridor. Respiratory distress is very apt to be made worse during or immediately after the swallow-

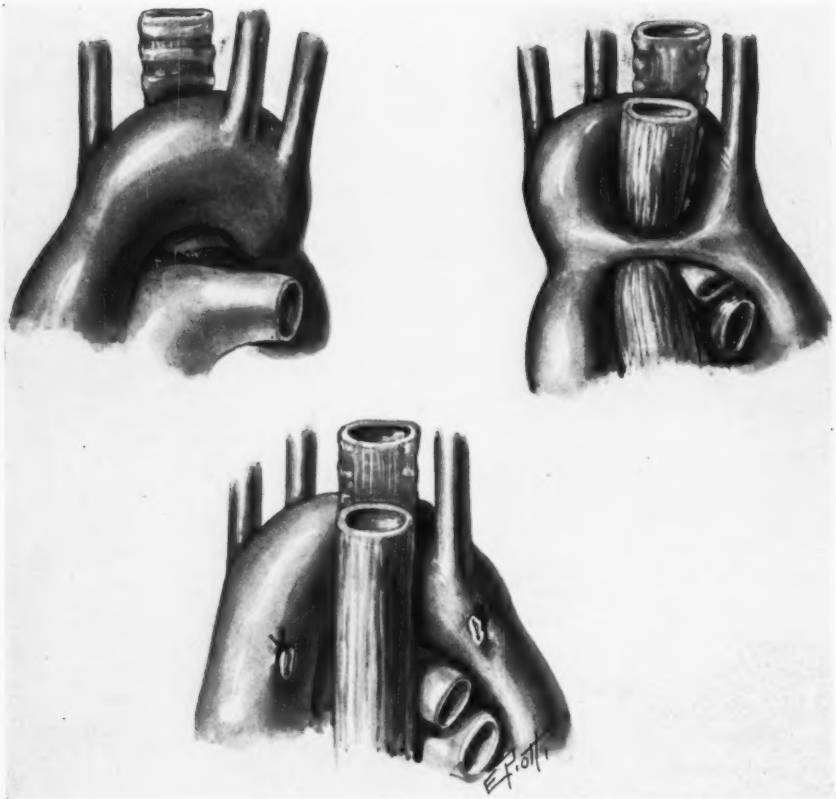

FIG. 2. Double aortic arch with large anterior limb and a smaller posterior limb, producing compression of the trachea and esophagus. *Above*. The two drawings show the anterior and posterior views of the anomaly. *Below*. Treatment of the condition by division of the small posterior arch, thus returning all structures to normal.

ing of milk or food. In severe cases, symptoms are serious enough to demand oxygen therapy. These babies are prone to lie with their heads in hyperextension, a position which tends to attenuate the trachea and push away from its anterior surface any structure which is impinging upon it. If the examiner forceably straightens the head, or flexes it toward the sternum, the exchange of air is reduced or can even be completely shut off, though the respiratory movements of the thorax continue.

Roentgenographic Findings. Roentgenograms of the chest may show some pneumonitis, if they happen to be taken at a time when there is superimposed lung infection. Films taken during inspiration may indicate poor or irregular aeration of the lungs, whereas during expiration there is apt to be an appearance of hyperaeration. Lateral films, if made at the correct exposure, can frequently outline the trachea by the air which it contains. Thus, without the use of a contrast medium, a fair appraisal can be made of the anteroposterior diameter of the trachea. While its upper portion is of normal caliber, the lower part has a markedly reduced lumen and the structure is apt to be displaced forward. A swallow of barium shows indentation of the posterior wall of the esophagus at the level of the third or fourth thoracic vertebra, this defect being nearly a horizontal one, and occurring at a level close to that where the tracheal compression is found. If further evidence regarding the status of the trachea appears to be desirable,

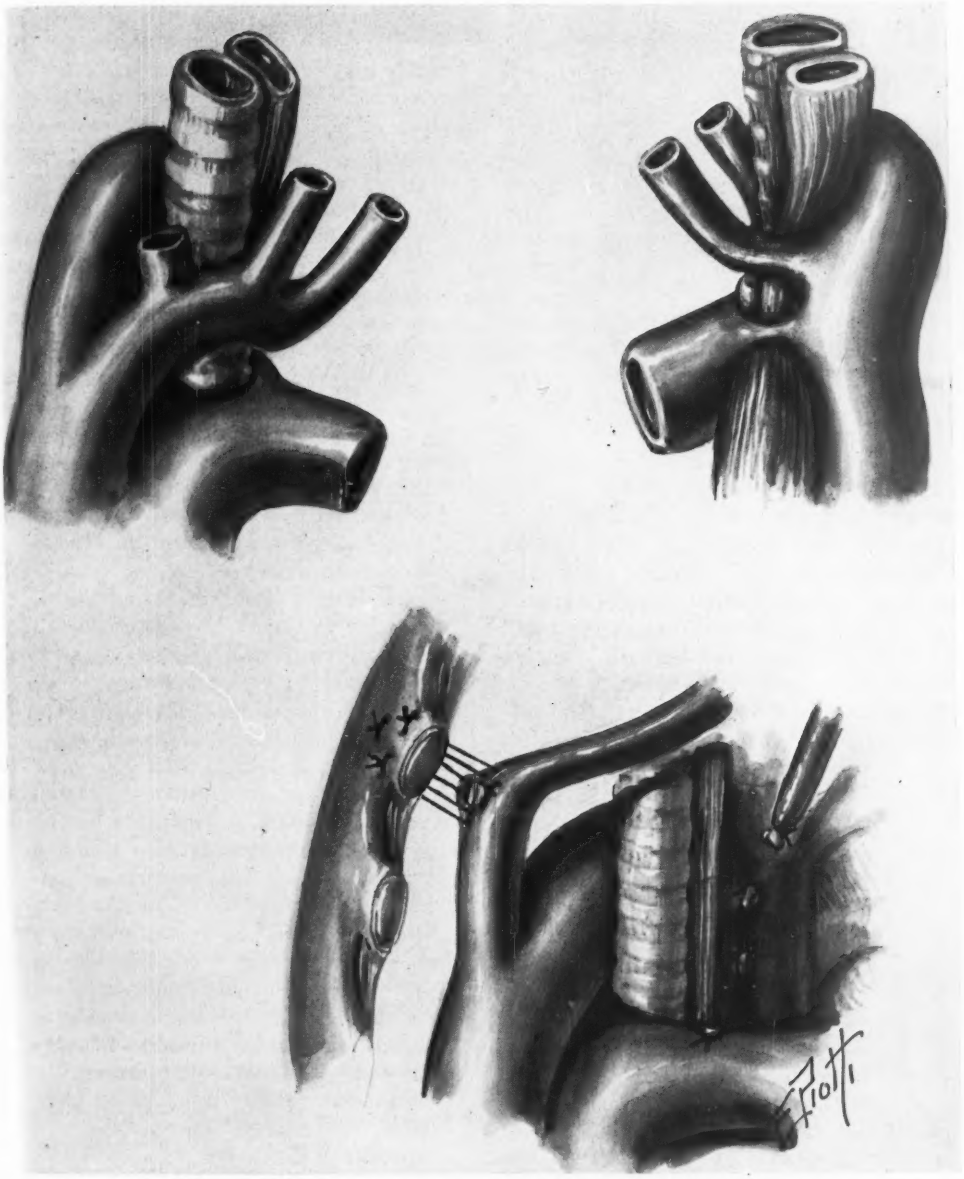

FIG. 3. Double aortic arch with the aorta descending on the right, constricting the trachea and esophagus. *Above.* Anterior and posterior drawings of the anomaly. The left arch is the smaller of the two. The ligamentum arteriosum between the pulmonary artery and the aorta also forms a part of the constricting mechanism. *Below.* Method of surgical therapy. The smaller left arch has been divided and cut away from the descending aorta; the left subclavian artery has been divided at its origin. The left common carotid artery has been tacked forward to keep it off of the trachea. The ligamentum arteriosum has also been cut.

this can be gained by lipiodol injection and delineation; for children under a year of age this can generally be done without anesthesia, but for older subjects it is best carried out under some form of general narcosis. Anteroposterior films show a definite compression of both sides of the trachea in its lower third; lateral views shows a constriction which is striking. This narrowing is at a level approximating that where the defect was found on the posterior wall of the esophagus. The combination of a posterior esophageal compression and an anterior tracheal defect (when found in the absence of a demonstrable mediastinal mass) is almost certain proof of some type of an encircling "vascular ring". The size of the posterior esophageal indentation is usually a fair indication of whether the posterior arch is the larger or the smaller of the two.

Surgical therapy. Surgery has much to offer these patients, because division of the smaller arch provides more room for the esophagus and particularly for the trachea. Without discussing the details of operative steps, the surgical solution of the problem is indicated in figs. 1, 2, and 3. Most commonly, it is the anterior arch which is the smaller of the two and thus is the one which must be severed. In a minority of cases, the posterior arch is the smaller and is the one which must be divided. In some cases the pulmonary artery has been held in a retrodisplaced position by virtue of its attachment to the aorta through the ligamentum arteriosum. This ligament should be divided, to allow the pulmonary artery to fall forward. While this additional step seems to have little value for some patients, it is certainly an important one for others.

Results of therapy. Of the 26 patients with double aortic arches who have come to operation, 16 had the aorta descending on the left and 10 on the right. Of the 16 with a left descending aorta, there were 11 in whom the left (anterior) arch was the smaller of the two and was accordingly divided, and there were five in whom the right (posterior) limb was the smaller one and was therefore sectioned. Of the 10 patients who had double arches and a right descending aorta, it was always the left (posterior) one which was severed. These 26 subjects ranged in age from one month to three years. There have been five deaths; two from hemorrhage at the operating table, one from cerebral edema the day following surgery (the child had been dangerously ill and in an oxygen tent for several months prior to surgical therapy), and two from pneumonia 3 and 10 days after operation. The 21 surviving patients have been followed for varying lengths of time, up to nine years, since operation. They have had extraordinary relief of symptoms. Usually, a marked improvement in the airway has been noted immediately after operation. In all instances, the exchange of air has obviously been more free, and the subjects have not had to use the accessory muscles of respiration for ordinary activity. Stridor has usually vanished, but in a few instances a trace of it remains. Postoperative tracheograms have usually shown marked improvement in size of the tracheal lumen after operation, but generally some deformity persists in the cartilages. It is reasonable to believe that the removal of all external pressure will give these tracheas a better chance to develop in future years as the children progress in body growth.

The overall results postoperatively have been exceedingly dramatic and have proved beyond a doubt that an operative attack on this vascular abnormality has great merit. This does not imply that all humans with a double aortic arch should necessarily be operated upon, because there are doubtlessly a few who tolerate the condition in a reasonably satisfactory way through a long life. However, it appears that most infants and young children with this abnormality are extremely apt to develop serious or even fatal complications at some subsequent time, and, hence, we feel that it is generally highly desirable to undertake surgical correction of the vascular anomaly whenever it is discovered.

Right Aortic Arch With Left Ligamentum Arteriosum

Pathologic anatomy. The first part of the ascending aorta lies in a normal position, but, instead of being directed upward and to the left in front of the trachea, it ascends and passes to the right of the trachea and the esophagus,

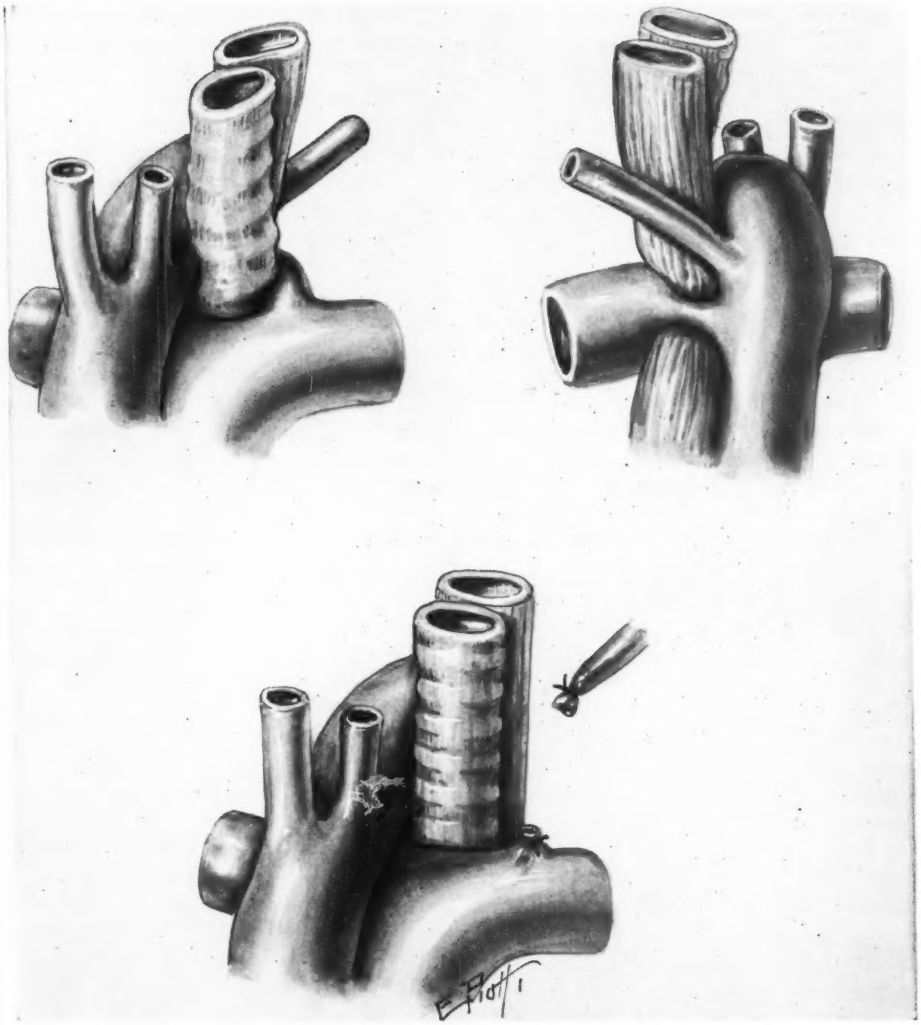

FIG. 4. Right aortic arch, with a left ligamentum arteriosum, producing compression of the trachea and esophagus. *Above*. Anterior and posterior views of the anomaly. *Below*. Surgical correction, by division of the ligamentum arteriosum and the first part of the left subclavian artery. These steps allow the trachea and esophagus to bulge to the left and to the rear.

and then continues as a descending aorta which may lie either to the left or to the right of the vertebral column. A right aortic arch in itself causes little or no disturbance, though at times it has been known to press on the right main bronchus or one of its branches and has led to pathologic changes in the lung. If the ligamentum arteriosum, or a patent ductus, runs from the pulmonary artery to the left of the trachea and the posterior aspect of the esophagus to join the descending aorta, this completes a constricting ring which encircles the esophagus and trachea (fig. 4). If this ring is sufficiently large, the functions of the esophagus and the trachea are not altered to any important degree, but if the ligamentum arteriosum is taut, the

space within the encircling structures is so small that the compressed esophagus, and especially the trachea, are greatly disturbed.

Clinical picture. With this anomaly, symptoms can develop quite similar to those which are produced by a double aortic arch, but generally are apt not to be quite so severe. As a rule, the onset of complaints is delayed until a bit later in childhood; the patients that we have encountered were on an average a few years older than those with a double aortic arch, the latter usually being seen in infancy. There may be a crowing type of respiration, some intercostal and suprasternal retraction, possibly recurrent pulmonary infection, and occasionally even some hesitancy in swallowing. The respiratory symptoms are generally aggravated during and following deglutition.

Roentgenographic findings. There may be evidence of pulmonary infection. There is a prominent shadow (aortic arch) projecting from the right side of the superior mediastinum. During inspiration there may be incomplete aeration of the lungs, and during expiration there may be hyperaeration, indicative of an obstruction somewhere above the carina. Lateral films of the chest, if appropriately exposed, can outline the air-filled trachea, showing the upper portion to be normal, whereas the lower segment is distinctly narrowed. Instillation of lipiodol into the trachea gives better visualization, shows a slight and rather elongated indentation of the right wall of the trachea, imposed by the adjacent aortic arch, indentation of the anterior surface of the trachea where the pulmonary artery is pulled against it, and a depression on the left side of the trachea from the ligamentum arteriosum. With a swallow of barium, one finds, at the same level as the tracheal defects were observed, that the esophagus has a narrow but very deep constriction in its left-lateral and posterior surfaces. Above this posterior notching of the esophagus, it is sometimes possible to identify a separate defect, passing obliquely upward and to the left, which is caused by the left subclavian artery which arises from the aorta and passes behind the esophagus to reach the left apex of the chest. By fluoroscopic and film studies, it is usually possible to recognize accurately this combination of vascular anomalies, but in some instances it is almost impossible to differentiate it from a double aortic arch which is combined with a right descending aorta.

Surgical therapy. Treatment of this condition is obviously one of alleviation and not of cure; it is impossible to shift the aortic arch from its right-sided bed, but we can divide the ligamentum arteriosum, which thus breaks the constricting "ring". The ligamentum arteriosum should also be divided. When these steps are properly performed, the pulmonary artery falls forward into a more normal position and sufficient room is given for the esophagus, and particularly the trachea, to drop backward and to the left. Whenever the left subclavian artery is found behind the esophagus, it, too, should be severed.

Results of therapy. Eighteen patients with this anomaly have been operated upon, the youngest two months and the oldest 12 years of age. There have been no deaths. The result in all subjects has been striking improvement. There has always been complete disappearance of any pre-existing dysphagia. There has been marked alleviation of respiratory distress which all subjects had prior to operation. In one of the older children, repeat tracheograms at the end of one year showed only disappointing growth of the tracheal rings in the involved area: this case emphasizes the desirability of carrying out these operations at an earlier time in life so that removal of all external pressure will give the trachea the best possible chance to enlarge during the growth period of the child.

It has long been known that a considerable number of humans possess a right aortic arch, but have few symptoms therefrom. Presumably, these have had a ligamentum arteriosum in front of the trachea or else this structure, even though it passes to the left and posterior aspects of the trachea and esophagus, has been very long and lax. In such instances operative intervention is not required. However, it is important to recognize those occasional individuals who do have a high degree of tracheal narrowing from one of the encirclements under discussion, because it is in this group that surgical therapy is a procedure of great value, particularly when it is performed early in life

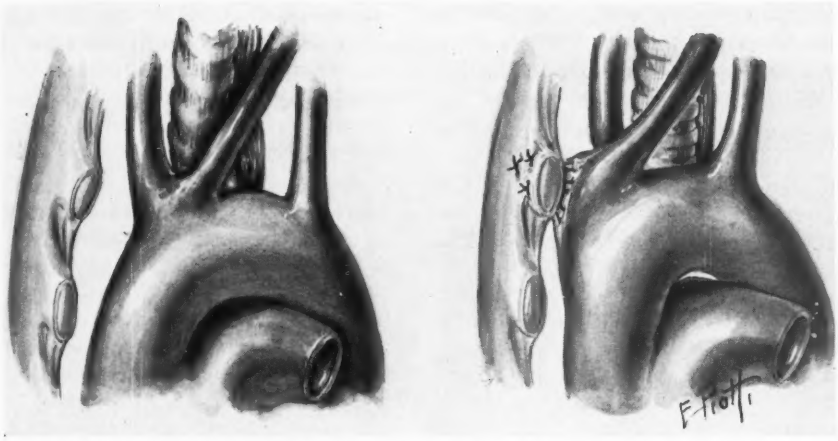

FIG. 5. Compression of the trachea by an anomalous origin of the innominate artery (or the left common carotid artery) from the aortic arch. *Left*. Drawing showing pressure on anterior surface of trachea by an anomalous left common carotid artery. *Right*. Alleviation of the tracheal compression by grasping advential structures of the offending vessels and drawing them to the sternum.

before the tracheal wall has become permanently deformed.

ANOMALOUS INNOMINATE ARTERY

Pathologic anatomy. The innominate artery can originate at a point farther along on the arch than is normal; when it does so, it must wind around the anterior surface of the trachea as it courses upward and to the right, to reach the right apex of the chest. If this vessel is large and taut, it can compress the trachea to a serious degree (fig. 5). While the pathologic anatomy is seemingly only a minor variation from normal and would appear to be of little consequence, the severity of symptoms which can accompany it has been emphasized by several patients who have been studied and found to have this anomaly.

Clinical picture. There can be inspiratory and expiratory crow of considerable degree, intercostal and suprasternal retraction, marked dyspnea, and even superimposed pneumonitis. Tracheal compression can be sufficiently severe to require the use of an oxygen tent. The head is apt to be held in hyperextension, which apparently improves the exchange of air for the child. There is no hesitancy in swallowing, nor are the respiratory symptoms made worse during feeding.

Roentgenographic findings. By roentgenologic study, the esophagus is entirely normal. The aortic arch is normal in size and in position. Visualization of the trachea may show little in the anteroposterior view, but lateral projections indicate a considerable narrowing in its lower third, the indentation appearing entirely on the anterior wall, whereas the posterior wall is straight and in normal alignment. It may be exceedingly difficult, or indeed impossible, to determine whether the base of the innominate artery or the base of the left common carotid artery (described in the next section) is at fault, but in some instances the obliquity of the anterior tracheal defect suggests which of these vessels is the offending one. In the absence of any anterior mediastinal shadow (such as a cyst or neoplasm) a tracheal defect of this sort certainly suggests some abnormal blood vessel in the region as a cause of the trouble. Any narrowing of the trachea which hints of the presence of an abnormal blood vessel of this sort can raise the question of whether the diminished lumen of the trachea is dependent upon incomplete development of its tracheal cartilages. Data on this point can be gathered from direct tracheoscopy and also by serial observations made roentgenologically throughout the respiratory cycle. If the tracheal defect is due to some external pressure, the narrowing remains relatively constant throughout the respiratory cycle; if the narrowing is due to deficient cartilagenous rings, the caliber

of the trachea will increase during inspiration and decrease during expiration.

Surgical therapy. After dissecting off and discarding the thymus, it is possible to view the aortic arch and the vessels in question. The base of the innominate artery can be seen wrapped around the anterior surface of the trachea, causing a decided indentation. Because of possible consequent brain damage, the offending vessel should not be severed. However, the first part of this artery and the accompanying aortic arch can be drawn forward by sutures taken through their adventitias and the surrounding soft tissues and running these silk sutures forward through the substance of the sternum. Appropriate tension on these silk sutures draws the vessels forward and thus carries them away from the trachea, thereby completely relieving the preexisting external pressure (fig. 5). These maneuvers are relatively easy to perform.

Results of therapy. Nine patients, all under one year of age, have been operated upon; there have been no deaths. The results of these undertakings have been very gratifying. The first patient had previously been hospitalized for four months because of severe respiratory distress; she was discharged eight days after operation, completely free of symptoms. The other patients have likewise been dramatically relieved of their respiratory complaints.

Anomalous Left Common Carotid Artery

Pathologic anatomy. This malformation is probably very rare. It is somewhat akin to the anomalous innominate artery described in the last section. The vessel is of normal size and distribution, but has an origin which permits it to branch off of the aortic arch more to the patient's right than is normal (fig. 6). It must therefore wind around the anterior surface of the trachea as it courses upward and to the left, to reach the left apex of the chest.

Clinical picture. The symptoms produced will obviously depend upon the degree of pressure which is exerted upon the front of the trachea. There may be moderate respiratory distress, some crowing during respiratory movements, dyspnea of mild to moderate degree, and possibly bouts of pulmonary infection. There are no disturbances in swallowing.

Roentgenologic findings. By roentgenographic examination, the findings are quite similar to,

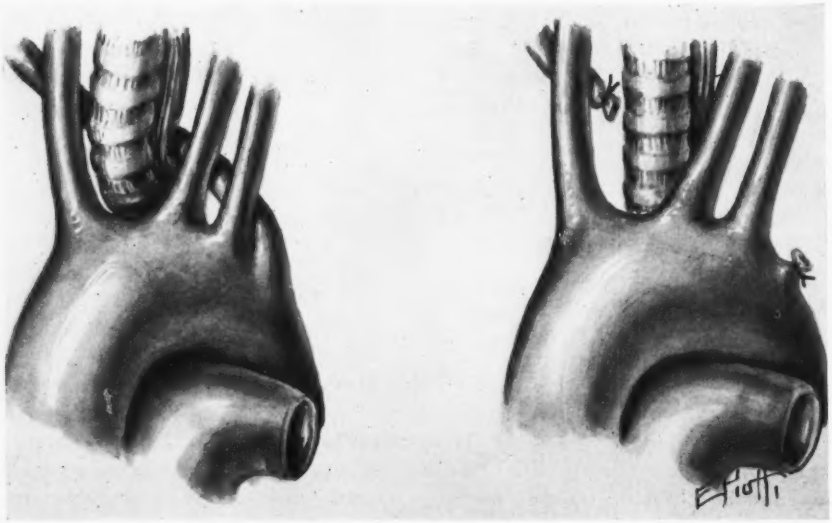

Fig. 6. Aberrant right subclavian artery, producing "dysphagia lusoria" by posterior compression of the esophagus. The right subclavian artery, instead of arising normally from the innominate artery, has an abnormal origin from the descending aorta, from which it courses upward and to the patient's right to emerge from the chest. *Left.* Drawing of the malformation. *Right.* Treatment of the dysphagia by ligation and division of the aberrant right subclavian artery.

and often indistinguishable from those described in the last section for anomalous innominate artery. The esophagus is normal by barium study. The trachea has a posterior wall which is sharp, distinct, and of normal contour and position, whereas the anterior surface of the trachea shows an indentation just at or above the level of the aortic arch, there being no anterior mediastinal cyst or tumor to account for these changes. Films taken at various angles may show that the tracheal defect is a grooved one, running upward and obliquely to the left, and strongly suggesting that the indentation is due to the unusual origin and pressure of the left common carotid artery. However, it is often difficult to see that such an obliquity exists, and hence the roentgenologist may not be able to determine which vessel is the offending one.

Surgical therapy. The surgical treatment for this condition is similar to that described in the last section for anomalous innominate artery. The first part of the left common carotid artery impinges against the trachea; this could be relieved by division of the vessel, but the chances of producing cerebral ischemia are so great that this maneuver should be avoided. The therapy consists of pulling the carotid artery and the adjacent portion of the aortic arch forward with mattress sutures which pierce the substance of the sternum. Appropriate tension applied through these silk sutures draws the common carotid artery and the arch forward so that they no longer are in contact with the trachea.

Results of therapy. Five patients have been subjected to this undertaking. In each instance, there has been complete relief of the preexisting respiratory symptoms.

Aberrant Right Subclavian Artery

Pathologic anatomy. As long ago as 1794, Bayford gave a fascinating description of the clinical picture and the relevant pathology in a case of an aberrant right subclavian artery which produced "dysphagia lusoria". The right subclavian artery, instead of arising in a normal fashion from the innominate artery, takes off independently from the distal part of the aortic arch. It then ascends and passes towards the right, to reach the right apex of the chest. It is rare for this artery to course in front of the trachea and it is uncommon for it to pass between the trachea and esophagus. In the majority of cases, it runs behind the esophagus in its upward path.

Clinical picture. An aberrant right subclavian artery is often recognized by radiologists who see a posterior indentation of the esophagus during barium studies of the alimentary tract. In a very high percentage of subjects there have been no important disturbances in the swallowing function. However, in a few cases, the subclavian artery can stretch sufficiently taut around the esophagus so that the peristaltic wave in the latter is altered and the patient experiences hesitation in swallowing which may be bothersome and indeed can interfere with the nutrition because of the diminished intake of food. In babies, delay in swallowing can be found in the early months of life. The subject is hungry and is eager for food and will start to swallow in an apparently normal way; he then has difficulty in getting the bolus started along the esophageal pathway. Some of the food or milk may pass downward, while the remainder stays in the pharynx for a considerable period of time, or is expectorated. Some of these patients have no delay in the swallowing of milk or other fluids, but do encounter difficulty when solid or semisolid food is later added to the diet. At no time is there respiratory distress, but some aspiration of material while attempting to swallow is not uncommon, so that gurgling or noisy respirations appear at such times.

Roentgenographic findings. By roentgenographic examination, the abnormality can be identified quickly and with certainty. The aortic arch is normal in size, position, and direction. The trachea shows no abnormality. With a swallow of barium, the lateral view shows a defect of rather small caliber on the posterior wall of the esophagus at the level of the third or fourth thoracic vertebra. By anteroposterior view, this indentation runs obliquely upward and towards the patient's right, the direction and position of this defect being in a line from a distal part of the aortic arch to the right apex of the chest. There is usually little or no ballooning of the esophagus above this zone, but a delay in the passage of

barium is often observed, due to an interference with progression of the peristaltic wave.

Surgical therapy. The surgical undertaking for the treatment of dysphagia lusoria is a rather simple one. It consists merely of exploration of the posterior mediastinum, freeing the anomalous artery from its bed, doubly ligating and dividing it. There are always sufficient collateral vessels to provide an adequate supply of blood to the right arm.

Results of therapy. In our series, 12 patients have been operated upon; these varied in age from three weeks to six years. All subjects survived this surgery and in each instance there was complete disappearance of the dysphagia which had existed prior to operation.

Summary

In recent years observations have shown that there are certain arterial malformations in the superior mediastinum which bring about significant compression of either the trachea or esophagus, or both of these structures. If the arterial derangements are of such a nature that symptoms are produced by obstruction of the esophagus and particularly by the impairment of the tracheal airway, it is of prime importance to recognize the underlying vascular malformation because surgical approach to the problem has a great deal to offer either by division of an offending vessel or by displacement of an artery in such a manner that more room is provided for the esophagus and trachea.

Roentgenographic examination of the esophagus and trachea with contrast media usually gives a fairly clear impression of the arterial derangement and leads to accurate diagnosis. Visualization of the aortic pathways by angiocardiography or by retrograde aortography is seldom necessary.

At operation, all these anomalies can be exposed through a left anterolateral transpleural approach to the superior mediastinum. Most of the thymus gland can be dissected off and discarded, allowing good visualization of the region.

Emphasis must be placed upon the fact that constrictions of the esophagus or trachea are not caused solely by vessels or ligaments, but that constriction is likewise produced by fibrous bands or sheaths which accompany these vessels and ligaments. Hence, it is important, not only to divide or displace the appropriate vessel or ligament, but also to cut any strands or bands of tissue which accompany these structures and which form a part of a constricting mechanism.

In a series of cases in which surgical therapy has been undertaken for alleviating compression of the esophagus or trachea for the various vascular anomalies under consideration, it has been shown that the risks of surgery can be kept relatively low and that the benefits which accrue from such treatment are real and well worth seeking.

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ABSTRACTS

ELECTROCARDIOGRAPHY

Klakeg, C. H., and Parkin, T. W.: Elevation of the RS-T Segment in the Precordial Electrocardiogram and Ventricular Extrasystoles after Exercise. Proc. Staff Meet., Mayo Clin. **29:** 97 (Feb.), 1954.

Elevation of the RS-T segment in a precordial electrocardiogram taken on a patient after exercise is reported. Transient paroxysmal ventricular tachycardia also was observed to occur after exercise, with complexes consistent with their origin in the injury zone or its border.

While no permanent ill effect from the exercise in the patient occurred, it is believed that the nature of the transient electrocardiographic changes should be classified empirically as of potentially serious nature. This single case should add evidence to the belief that an exercise test, particularly if it is an extensive one, is not without danger, and that patients undergoing the test should be carefully chosen and supervised during the procedure.

SIMON

Pulvertaft, C. N.: Electrocardiographic Changes in the Dumping Syndrome. Lancet **6806:** 337 (Feb. 13), 1954.

The vasomotor symptoms of dumping were investigated electrocardiographically. Fourteen patients exhibited symptoms during the test, all of whom showed electrocardiographic changes. Twelve did not experience symptoms during the test. One of these showed flattening, and five slight lowering, of the T wave, whereas the remaining six showed no changes. In the seven symptom-free patients no electrocardiographic changes were found. The typical electrocardiographic changes were a lowering or flattening of the T wave, usually associated with an exaggerated U wave, which encroached on T. Other changes were inversion of the T wave, sagging of the S-T segment and an increase in height of the P wave.

The electrocardiographic changes are related to the rate of absorption of sugar. The nature of the electrocardiographic changes has not yet been established, but very similar changes can be produced by subcutaneous or intravenous injection of adrenaline, and there is some evidence that adrenal stimulation plays a part in this syndrome.

BERNSTEIN

Beyadjian, N., and Dechamps, G.: The Absence of Alteration of the QRS Axis with the Development of Intraventricular Block. Acta cardiol. **9:** 127 (Fasc. 2), 1954.

In 200 cases of intermittent intraventricular block reported in the literature, the electrocardiographic patterns before and after the development of the conduction defect were compared. In 81 per cent, the QRS axis did not change but QRS became smaller in amplitude when the block appeared. In the majority of cases, a left-sided block occurred with pre-existent left axis deviation, and a right-sided block with pre-existent right axis deviation. The manifestation of the block is usually related to an increase in heart rate. Thus, according to this study, an intraventricular block does not alter the electrical axis. On the contrary, its direction during block seems to depend on the original contour of the ventricular complex.

PICK

Schwartz, W. B., Levine, H. D., and Relman, A. S.: The Electrocardiogram in Potassium Depletion. Its Relation to the Total Potassium Deficit and the Serum Concentration. Am. J. Med. **16:** 395 (Mar.), 1954.

On the basis of 14 balance studies on 11 subjects with varying degrees of potassium depletion resulting from diarrhea, or from the administration of desoxycorticosterone acetate, compound F, or acidifying salts, the authors conclude that the electrocardiogram cannot be relied upon as a guide to diagnosis or therapy in potassium depletion of moderate severity. The electrocardiogram was consistently related neither to the total potassium deficit nor to the serum potassium concentration. No conclusions were drawn about the relationship of the electrocardiogram to intramyocardial potassium concentration.

In only half the observations on subjects depleted of 40 to 550 mEq. of potassium did the electrocardiogram show evidence of potassium depletion. The electrocardiogram was often normal with low serum potassium concentrations and conversely was sometimes abnormal with normal serum concentrations. When changes occurred in the electrocardiogram, they were not quantitatively related to either the potassium deficit or the reduction in serum concentration. There was sometimes a lag of one or more days in the electrocardiographic response to acute loss or retention of potassium. Only in the subjects given compound F were there significant losses of nitrogen, and in these cases the uncorrected potassium balance was better correlated with the electrocardiogram than was the balance corrected for nitrogen. None of the patients with acidosis developed electrocardiographic evidences of potassium depletion.

HARRIS

Blomberg, L., and Lindgvist, T.: The Electrocardiogram in Paroxysmal Essential Hypopotassemia (Periodic Paralysis). Acta med. scandinav. **147:** 437 (Fasc. 5–6), 1954.

The electrocardiographic changes in two cases of periodic paralysis are reported with correlations with the changes in the serum potassium levels. Both patients showed flattening of the T waves and depression of the RS-T segments during the seizures. In one case the QRS complex was also slightly widened during the attack and the Q-T interval was prolonged. In the second case a definite U wave was present during the attack. All abnormalities disappeared in the first case after administration of potassium chloride and no evidence of hyperpotassemia appeared even though the blood level reached 30 mg. per 100 cc. In the second case some peaking of the T waves and elevation of the S-T segments appeared during the administration of potassium chloride, even when the serum potassium did not go above the normal level.

ROSENBAUM

Smyth, A. G., and Powell, G. M.: The Electrocardiogram in Hemorrhagic Fever. Am. Heart J. **47:** 218 (Feb.), 1954.

One hundred forty-seven electrocardiograms from 55 cases of hemorrhagic fever taken during the acute stages of the disease, and 90 electrocardiograms from 78 cases in the convalescent stage of the disease have been reviewed and correlated with significant clinical findings. Abnormalities or suggestive abnormalities were noted in one or more tracings of 27 of the 55 cases in the acute series. These abnormalities included hyperkalemic effects, prolongation of the Q-T interval, sinus bradycardia, multiple auricular premature beats, nonspecific negative T-waves, left bundle-branch block, right bundle-branch block, and RS-T segment elevation. Seven of the 78 cases in the convalescent series showed variations from normal. In four of the seven, the changes were slight and of questionable significance. The other three include one case each of right bundle-branch block, auricular fibrillation, and nonspecific but marked T-wave inversions. However, in the last case serial study revealed a definite progression towards normal. Therefore, only two cases in the series provide evidence that permanent electrocardiographic abnormality results from hemorrhagic fever. Even in these it is impossible to be certain that the abnormality did not antedate the illness. In addition, long-term follow-up may reveal a return to normal.

RINZLER

Kreutzer, R., Caprile, J. A., Berre, G. G., and Becu, L. M.: The Electrocardiogram in Tricuspid Atresia. Arch. mal. coeur **47:** 113 (Feb.), 1954.

The authors observed an anatomically proven case of tricuspid atresia without the characteristic left axis deviation in the electrocardiogram. Because of this apparent failure of an important diagnostic criterion, electrocardiograms were reviewed of other cyanotic congenital malformations, 15 of which had tricuspid atresia proven either by autopsy or by angiocardiography. The conclusions derived from this study were as follows:

Except for rare instances with an electrically vertical position, left axis shift in the standard leads is ordinarily found in the presence of tricuspid atresia. However, other cyanotic lesions such as transposition of the great vessels or a truncus communis with a common ventricle may produce a similar electrocardiographic pattern. In tricuspid atresia the P waves are usually very tall, particularly in lead II. There is no correlation between the finding of a left heart strain pattern and the size of the heart. Rs complexes in the right precordial leads can be attributed to hypertrophy of the ventricular septum or to the thickness of the wall of the hypoplastic right ventricle. The authors ascribe great importance to the measurement of the intrinsicoid deflection in precordial as well as unipolar limb leads because by this method, left ventricular hypertrophy can be demonstrated in

lead aV_F even in the presence of a right axis deviation in the standard leads.

PICK

Corsi, V., and Sangiorgi, M.: Changes of the S-T Tract Following Experimental Lesions of the Atrial Wall. Cuore e circolaz. **38:** 245, 1953.

Atrial alterations may modify the S-T tract of the electrocardiogram through abnormalities of the Ta wave which is usually buried within the ventricular complex.

An experimental study was made in dogs following cauterization of the posterior wall of the left atrium. S-T depression was attributed to delayed onset of the atrial injury currents. Direct tracings from the epicardial surface of the injured atrium confirmed that the atrial injury current lasted 0.25 second or more.

S-T changes observed in clinical cases in conjunction with P-Q alterations are probably due to atrial lesions.

LUISADA

Wolff, F., Richman, J. I., and Soffe, A. M.: The Effect of Heart Position and Rotation on the Cardiac Vector: An Experimental Study. Am. Heart J. **47:** 161 (Feb.), 1954.

An experimental method has been devised for studying the effect of heart position and rotation on the cardiac vector. The spatial positions of the initial and terminal vectors are characteristic for various heart positions and degrees of rotation. The width of the QRS loop in each projection is related to the degree and kind of rotation of the loop about its longitudinal axis, as well as to intrinsic changes of the loop. The spatial position of the initial vectors can be utilized to determine heart position, and for the differentiation of the normal heart, right ventricular hypertrophy, left ventricular hypertrophy, combined ventricular hypertrophy, myocardial infarction, and left bundle-branch block. The spatial position of the terminal vectors can be utilized to distinguish between left ventricular hypertrophy and incomplete right bundle-branch block, and between the normal but unusually rotated heart and incomplete right bundle-branch block. The spatial position of the terminal vectors can be utilized to determine position and rotation of the heart, even when the initial vectors are not suitable for this purpose as a consequence of having been altered by localized myocardial disease.

RINZLER

Roehm, D. C., Kory, R. C., Mabe, R. E., Townes, A. S., and Meneely, G. R.: Duration of the Q-T Interval During the Anoxemia Test. Am. Heart J. **47:** 204 (Feb.), 1954.

The Levy anoxemia test was studied in 40 normal men and 95 patients with duration of electrical systole as measured by the corrected Q-T interval ($Q\text{-}T_c$). Initial $Q\text{-}T_c$ durations were significantly higher in patients with angina pectoris, as a group, than in controls. During the anoxemia test, the prolongation of $Q\text{-}T_c$ was much greater in patients with angina than in normal subjects and in patients with chest pain of noncardiac origin. When the maximal increase in $Q\text{-}T_c$ during the anoxemia test is plotted against the control (initial) $Q\text{-}T_c$ value for all subjects and patients, it is found that an oblique line may be drawn which separates nearly all of the patients with true angina pectoris from nearly all of those without it. The equation representing this line of separation is

$$0.480 \text{ second} = (\text{initial } Q\text{-}T_c) + 2.6\ (\text{maximal increase in } Q\text{-}T_c)$$

For simplicity in clinical application, it can be stated that 0.480 is the "upper limit of normal" for men of a value computed by adding 2.6 times the maximal increase of $Q\text{-}T_c$ during anoxia to the initial $Q\text{-}T_c$ duration. The value so determined is termed the "Q-T Anoxemia Index." Of two observed "false-positive" Levy anoxemia tests, one case in which hyperventilation was causative also demonstrated an abnormal $Q\text{-}T_c$ response. The other in whom the RS-T, T-wave abnormalities are considered a residuum of recent pericarditis, showed a normal "Q-T Anoxemia Index." These observations suggest that the alteration of $Q\text{-}T_c$ duration during the course of the anoxemia test may be an additional aid in distinguishing a normal from an abnormal response since 89.5 per cent of patients considered to have true angina pectoris exhibited positive tests by the Q-T anoxemia index criterion, in contrast to only 55.2 per cent positive by the Levy criteria, while the incidence of false positives was not significantly increased.

RINZLER

Jones, G.: Paroxysmal Auricular Tachycardia: Observations in 47 Cases. Ann. Int. Med. **40:** 581 (March), 1954.

Paroxysmal auricular tachycardia, as seen in 47 cases in the author's private practice, has been summarized. These cases include five patients with the Wolff-Parkinson-White syndrome, and four others with a probable variant of the same. The high associated incidence of anxiety states is noted. Reassurance and explanation were considered the most important things to be done for the majority of patients. In only 7 of 47 patients was specific medication necessary. In these the quick acting digitalis glycosides seemed the drug of choice in stopping the tachycardia in most instances. Quinidine was the best preventive. The prognosis would seem good, except in untreated patients in infancy and in people with coincidentally acquired heart disease. Rhabdomyoma of the heart may express itself in infants by episodes of paroxysmal auricular

tachycardia. Of the two patients showing definite myocardial disease in this series, one had coarctation of the aorta and the other hypertensive heart disease.

WENDKOS

ENDOCRINE EFFECTS ON CIRCULATION

Wyman, L. C., Fulton, G. P., Shulman, M. H., and Smith, L. L.: Vasoconstriction in the Cheek Pouch of the Hamster Following Treatment with Cortisone. Am. J. Physiol. **176:** 335 (Feb.), 1954.

Cortisone acetate produces vasoconstriction in the cheek pouch vessels which appears after a delay of nine days. The time course of appearance and disappearance was the same for single and repeated doses. The blood pressures were normal and there was no change in mesoappendix vessels at the time at which the cheek pouch vessels were constricted.

OPPENHEIMER

Svanborg, A., Birke, G., and Plantin, L. O.: Adrenal Function and Hyperlipemia in Nephrosis and Diabetic Nephropathy. Acta med. scandinav. **148:** 73 (Fasc. 1), 1954.

An investigation of adrenal activity in five cases of nephrosis with severe hyperlipemia, four cases of diabetic nephropathy and one dog with hyperlipemia following bilateral ureteral ligation was carried out. This was done because certain observations have suggested that lipid metabolism may be affected by alterations in adrenal activity. The compound F concentration was found to be normal in all cases. Fractionation of the urinary 17-ketosteroids in two cases of nephrosis gave normal results. Studies of the compound F concentration before and after corticotropin administration showed no evidence of increased adrenal activity. The authors conclude that these observations disclosed no evidence suggesting that the hyperlipemia of nephrosis or diabetic nephropathy is due to impaired adrenal activity.

ROSENBAUM

Böttiger, L. E.: Hypopotassemia in Hyperparathyroidism. Acta med. scandinav. **148:** 51 (Fasc. 1) 1954.

The report is concerned with a woman aged 67 years who had renal calculi, arthritic complaints, generalized osteoporosis, a blood potassium level of 12.5 mg. per cent and a blood calcium level of 15 mg. per cent. A parathyroid adenoma was found to be responsible, and its removal was followed by marked symptomatic improvement. The electrocardiogram is said by the author to show changes typical of hypopotassemia and hypercalcemia. The electrocardiographic changes cleared temporarily after a single oral dose of 10 Gm. of potassium chloride, and they cleared permanently after surgical removal of the parathyroid adenoma.

ROSENBAUM

HYPERTENSION

Enderle, J., Cleempoel, H., Van Wien, A., and Gatez, P.: Two Cases of False Positive Regitin Tests in Hypertensives without Pheochromocytoma. Acta cardiol. **9:** 149 (Fasc. 2), 1954.

The authors review the methods currently used in the diagnosis of pheochromocytoma and report two false positive tests in two hypertensive females. Both cases had an arteriosclerotic brain lesion and significant renal alterations, which in one caused an elevation of the blood urea level. In one, a retropneumoperitoneum suggested the presence of a left suprarenal mass, which, however, was not found at surgical exploration. In both cases, the absence of abnormal chromaffine tissue was ascertained at autopsy.

PICK

Hamilton, M., Pickering, G. W., Fraser Roberts, J. A., and Sowry, G. S. C.: The Aetiology of Essential Hypertension. 2. Scores for Arterial Blood Pressures Adjusted for Differences in Age and Sex. Clin. Sc. **13:** 37 (Feb.), 1954.

The authors present a method of calculating adjusted scores for arterial pressure which allow for differences in age and sex. The fitting of curves for blood pressure levels at various ages in both sexes was described in a previous paper. The extent of deviations from the expected norm for age and sex is obtained in units of 5 mm. Statistical methods are given for calculating the regressions of variance of arterial pressure on age. The deviations are then adjusted to the corresponding deviation as at age 60, which is chosen as the standard age. Tables are given for calculating age and sex adjusted scores. These calculations show that departures from normality do not show any appreciable association with age.

ENSELBERG

Hamilton, M., Pickering, G. W., Fraser Roberts, J. A., and Sowry, G. S. C.: The Aetiology of Essential Hypertension. 1. The Arterial Pressure in the General Population. Clin. Sc. **13:** 11 (Feb.), 1954.

Casual, rather than basal, blood pressures were measured in patients attending clinics for the treatment of illnesses not connected with hypertension. The total number of persons studied was 2031, of ages 10 to 85 years. It was demonstrated that the average arterial pressure rose with age, the growth curve for systolic pressure being curvilinear and for diastolic pressure, linear. Systolic pressures were higher in men up to the age of 30, and thereafter higher in women. Diastolic pressures were higher in women at all ages, and the rate of

rise of blood pressure with age was also steeper in women. The rate of rise with age showed considerable individual variability.

The authors emphasize that there is no natural dividing line between normal and abnormal pressure and that in every decade the series showed continuity. What is termed essential hypertension represents not a discrete clinical entity but rather that segment of the population in which the arterial pressure exceeds an arbitrary level and in which no other disease can be found to account for the observed pressure.

ENSELBERG

Wilkins, R. W., Judson, W. E., Stone, R. W., Hollander, W., Huckabee, W. E., and Friedman, I. H.: Reserpine in the Treatment of Hypertension. A Note on the Relative Dosage and Effects. New England J. Med. **250:** 477 (Mar. 18), 1954.

Reserpine, a pure alkaloid of Rauwolfia serpentina was compared clinically with the crude drug. Reserpine was found to be an agent with modest hypotensive and bradycrotic action closely resembling Rauwolfia. Its side effects, including sedation, nasal congestion, weight gain, diarrhea, nightmares and depression were very similar to those of the crude drug. The total daily dosage tolerated ranged between 0.1 and 1.0 mg. It was found that 0.1 mg. of Reserpine was not less active in any respect than 100 mg. of the crude roots of Rauwolfia. It was concluded that Reserpine is the chief active principle of crude Rauwolfia. In hypertensive patients Reserpine relieved headache, dizziness and fullness in the head, decreased palpitation, lessened nervousness, irritability and anxiety. This drug also seems to be of value in combination with other hypotensive agents.

ROSENBAUM

Muirhead, E. E., and Shields, W. F.: Erythrophagocytosis and Hemosiderosis in Lymph Nodes, Spleen and Liver in Patients Dying of Malignant Hypertension, Chronic Glomerulonephritis and Pyelonephritis and Polycystic Disease. Ann. Int. Med. **40:** 307 (Feb.), 1954.

Morphologic changes within reticuloendothelial structures (hemorrhages, erythrophagocytosis and nemosiderosis of lymph nodes, erythrophagocytosis and hemosiderosis of the spleen, and hemosiderosis of the liver) have been observed in 20 of 21 cases of advanced bilateral renal disease associated with the clinical triad of hypertension, renal insufficiency and anemia. Similar findings were noted in three of seven nonanemic cases. These findings are similar to those previously described in experimental uremia associated with a hemolytic anemia. It is suggested that in some instances these changes may be related to the pathogenesis of the anemia of uremia in man.

WENDKOS

Bohle, A.: A Critical Contribution to the Morphology of an Endocrine Renal Function and its Significance for Hypertension. Arch. Kreislaufforsch. **20:** 193 (Mar.), 1954.

In order to test the validity of concepts which imply structural alterations of the kidney as evidence of a disturbance of its endocrine function in hypertension, the authors produced hypertension in rats by several experimental methods and compared histologic findings in the kidneys of such animals with findings in normal and hypertensive patients.

Following clamping of the aorta, epithelioid cells in afferent vessels increase in number and decrease after wrapping the kidney in plastic material. Such cells are found more often in kidneys of normotensive than hypertensive patients and seem to represent a reaction to reduction of renal blood flow rather than the actual site of renin formation. No histologic evidence was found of morphologic alterations restricted to contorted tubuli of first order, claimed by others to lead to formation of renin. However, in unilaterally nephrectomized hypertensive rats hyperplasia of the epithelium of tubuli of second order occurred, and the appearance of cells described by Becher was noted. The latter cells were also seen in increased number in kidneys of older people and of hypertensives. Such formations seem to represent another reaction of the kidneys to various stimuli, for example, hypertension, which conceivably might lead to the production of vasopressor substances.

After evaluation of all these data the authors arrived at the conclusion that, at the present, there is no definite morphologic proof to support the central role of the renin mechanism in the pathogenesis of hypertension.

PICK

Cotten, M. de V. Brown, J. M., and Kronen, P. S.: Heart Forces Responses to Pressor Amines during Hypotension Produced by Hexamethonium. Anesthesiology **15:** 126 (Mar.), 1954.

Six dogs were employed in this study. Each dog was previously prepared by suturing a strain gage arch to the anterior aspect of the right ventricle and inserting polyethylene tubings into the right femoral artery and vein. In the resting conscious animal and during the course of the experiments under anesthesia measurements of the heart force and femoral arterial pressures could thus be recorded. The administration of hexamethonium to lightly anesthetized animals was capable of producing a substantial fall in blood pressure and in cardiac contractile force and rate. After suitable hypotension had developed rapid intravenous administration of *l*-arterenol resulted in a substantial increase in the arterial pressure and the contractile force of the heart. In comparison, equipressor doses of methamphetamine and ephedrine produced only moderate

increments in the contractile cardiac force. The increase in contractile force of the heart resulting from *l*-arterenol, ephedrine, and methamphetamine is considered to represent actual drug-produced increases in heart force, but the small increments observed after phenylephrine and methoxamine are considered as responses to hypertension and not as the result of direct myocardial stimulation. The authors conclude that in conditions of hypotension associated with a weakened myocardium pressor amines such as *l*-arterenol, methamphetamine or ephedrine are indicated since they simultaneously increase the contractile force of the heart as well as increasing the arterial blood pressure.

SAGALL

Mandel, M. H., Greene, R. W., Sapirstein, L. A., and Ogden, Eric: Reduction of Mean Arterial Pressure in Dogs with Chronic Hypertension by Pentobarbital. Am. J. Physiol. **176:** 352 (Feb.), 1954.

Nembutal (25 mg. per kilogram intravenously or 30 mg. per kilogram intraperitoneally) lowers pressure in long-standing renal hypertensive dogs. This lowering takes place within the first hour after the anesthetic is given. Normotensive controls showed a rise in pressure.

OPPENHEIMER

Deming, Q. B.: Association of Polyuria and Albuminuria with Hypertension of Unilateral Renal Origin. Arch. Int. Med. **93:** 197 (Feb.), 1954.

A case is reported of a young woman in whom hypertension developed which was apparently relieved by removal of an atrophic kidney, distal to a diseased renal artery. Her initial symptoms were not those of hypertension, but those of polyuria and polydipsia. She also showed albuminuria, edema, and weight loss. The literature on experimental renal hypertension is reviewed to comment on the relationship between the induction of these symptoms and the induction of hypertension. A few case reports of hypertension cured by nephrectomy are reviewed to show that these renal effects are not uncommonly seen in human cases.

BERNSTEIN

PATHOLOGIC PHYSIOLOGY

Sarnoff, S. J., Case, R. B., Waithe, P. E., and Isaacs, J. P.: Insufficient Coronary Flow and Myocardial Failure as a Complicating Factor in Late Hemorrhagic Shock. Am. J. Physiol. **176:** 439 (Mar.), 1954.

When hypotension exists for some time, the left ventricle fails first and the right does so later. The signs of failure are a rise in atrial pressure, dilatation and decreased systole. Death is from ventricular fibrillation or ventricular standstill if nothing is done to prevent them. An increase in left coronary flow reverses the atrial pressure rise and the dilatation. This is so even though the blood pressure remains low and blood volume is not increased. Early observations with the sympathomimetic agent Aramine indicate that it may act in the same way as mechanically increased coronary flow. The authors remind us that myocardial failure due to reduced coronary flow plays an important role in hemorrhagic shock.

OPPENHEIMER

Brecher, G. A.: Cardiac Variations in Venous Return Studied with a New Bristle Flowmeter. Am. J. Physiol. **176:** 423 (March), 1954.

Blood flow in the superior vena cava is accelerated during ventricular systole when the tricuspid valves are closed. Increased atrial volume due to the descent of the atrioventricular junction is indicated, by means of simultaneous measurements of pressure and flow, as the cause of this increased acceleration. The author states that ventricular systole ejects blood into arteries and draws blood from veins into the atrium. Although ventricular diastole has little action on venous return, the increased negative intrathoracic pressure operating at this time on the atrioventricular walls has a powerful effect. Atrial systole stops or reverses flow in the central veins. Positive pressure lung inflation with the chest open increases this last mentioned effect. Flow in the superior vena cava is constant at varying heart rates. During bradycardia, 80 per cent of atrial inflow takes place during ventricular diastole, but in tachycardia, 80 per cent of atrial inflow occurs during ventricular systole. It is pointed out that this mechanism assures the venous return upon which cardiac output depends by shifting its atrial filling from a largely passive inflow during a long diastole of bradycardia to an active systolic attraction of venous blood during tachycardia.

OPPENHEIMER

Facquet, J., Alhomme, P., Lemoine, J. M., Colvez, and Lagadoux: The Left Atrial Pressure in Mitral Disease Determined by Transbronchial Access. Arch. mal. coeur. **47:** 137 (Feb.), 1954.

A previously reported method of recording the left atrial pressure curve by direct puncture of the chamber through a bronchus was used in 25 cases with mitral disease. Data thus obtained were compared with curves of normals and of hypertensives in left heart failure. The presence of a tachycardia over 100 per minute introduced a definite error into the evaluation of the tracings.

In mitral stenosis the mean left atrial pressure is high, and there is only little difference between systolic and diastolic pressures. Mitral insufficiency is suggested in the presence of sinus rhythm by a marked accentuation of the v wave, and in auricular fibrillation by the finding of a large difference between extreme pressure values. However, no anomaly of the pulse wave contour could be estab-

lished under the latter circumstances which would furnish valuable information.

The authors reached the conclusion that more experience is necessary to confirm the safety of the method and its value in the differential diagnosis of mitral lesions.

PICK

Haddy, F. J., Richards, A. G., Alden, J. L., and Visscher, M. B.: Small Vein and Artery Pressures in Normal and Edematous Extremities of Dogs under Local and General Anesthesia. Am. J. Physiol. **176:** 355 (Feb.), 1954.

Small subcutaneous vein pressures in the foot were 8 to 25 mm. Hg in unanesthetized dogs. These were about the same under pentobarbital. Since larger veins had higher pressures in the waking state, the gradient from small to large veins was greater under anesthesia. There were large variations in small vein pressures under local anesthesia, but large vein pressures were largely constant. The authors point out the possibility of nervous and humoral mechanisms controlling small vein pressures. Capillary pressures are not static. Exercise increased small vein pressures more than in large. Mean pressure for large arteries was 123 mm. Hg and for small (foot pad) was 65 mm. Hg. Arteriovenous fistulas of the hind legs elevated the gradient of small to large vein pressures in three of four dogs. When small vein pressure approached that of colloid osmotic pressure, edema was present.

OPPENHEIMER

Radner, S.: Suprasternal Puncture of the Left Atrium for Flow Studies. Acta med. scandinav. **148:** 57 (Fasc. 1), 1954.

The author describes a technic for direct puncture of the left atrium with a special double needle through the suprasternal fossa and through the space between the trachea and the aortic arch. The procedure was first performed on 50 cadavers and to date has been applied in five patients. The method is said to permit studies of the inflow hemodynamics of the left heart and recording of pressure curves from the left atrium. It is said that no complications of the method have been encountered.

ROSENBAUM

Roberts, B., Schnabel, T. G. Jr., and Ravdin, I. S.: Multiple Episodes of Cardiac Arrest. J. A. M. A. **154:** 581 (Feb. 13), 1954.

This is a report of successful restoration of cardiac function on four separate occasions in a single patient over a 10-day period. Thoracotomy and cardiac massage were carried out successfully twice in the same patient. On two occasions ventricular fibrillation was the cause of cessation of circulation. On two occasions a strong blow over the pericardium restored the respiration and pulse in the patient. It is suggested that several such blows with the fist be tried prior to thoracotomy and massage in attempts to restore circulation. Efforts to prevent recurrence here were unsuccessful and the patient died in her fifth attack. In this case the episodes of cardiac arrest may well have been related to depletion of intracellular potassium.

KITCHELL

Marshall, R., McIlroy, M. B., and Christie, R. V.: The Work of Breathing in Mitral Stenosis. Clin. Sc. **13:** 137 (Feb.), 1954.

The authors calculated the work of ventilating the lungs in patients with mitral stenosis, employing their previously reported method which uses simultaneous tracings of intraesophageal pressure and of tidal volume or of airflow. The advantage of intraesophageal pressure recording is that it obviates the need for inducing a pneumothorax in order to measure changes in intrathoracic pressure. From the data obtained, it is possible to calculate the work performed and the coefficient of elastic resistance.

Results obtained in patients with mitral stenosis show that in some patients at rest the coefficient of elastic resistance may be in the normal range, though it is often increased. However, on exercise this coefficient increases, whereas in normal subjects it decreases. The work of breathing in these patients while at rest is generally slightly increased above the normal range, but on exercise it is increased to two or three times the value in normal persons. This increase in work on exercise is due to the increase in elastic resistance which, in turn, is presumably caused by increased rigidity of the congested lungs.

Studies made on subjects lying flat indicate that in normal persons the work of breathing increases, but the elastic resistance is not changed. In patients with orthopnea there is an increase in elastic resistance and a marked increase in respiratory work. The severity of dyspnea and orthopnea appear to be proportional to the degree of pulmonary rigidity and consequently to the work required to ventilate. In general the sensation of dyspnea appears when the subject is doing 2 to 3 kilogram meters of respiratory work per minute. The rapid and shallow breathing of exertional dyspnea and the changes in orthopnea occur because the patient breathes at a rate and depth which is most economical in terms of respiratory work.

ENSELBERG

Comberiati, L., and Collicelli, A.: Modifications of the Phonocardiogram after Initial Commissurotomy. Arch. mal. coeur **47:** 268, 1954.

A phonocardiographic study of 34 patients with mitral stenosis was made before and after commissurotomy.

Decreased intensity of the loud first heart sound (22 out of 28) and of the loud second pulmonic sound (27 out of 34) was frequent. Splitting of the

second pulmonic sound nearly always disappeared while the opening snap frequently persisted even after surgical intervention. The diastolic rumble disappeared in all cases in the initial postoperative period but reappeared a few months later (7 out of 11) and reached the previous intensity in two cases.

A systolic murmur was recorded in 11 cases (faint in nine, loud in two). Following intervention, the murmur decreased in three, increased in two, and remained unchanged in six cases. Five patients who did not have a systolic murmur before commissurotomy, presented such a murmur after the procedure.

LUISADA

Marshall, L. H., and Hanna, C. H.: Differences in T-1824 and Cell Concentration of Venous Blood of Dogs after Dextran. Am. J. Physiol. **176:** 331 (Feb.), 1954.

In normal dogs, Dextran (10 ml. per kilogram) expands dye distribution volume in one-half hour to about one-third more than the volume injected. After three to four hours this same amount of Dextran expands the dye distribution volume between one-third and one-half the injected volume.

OPPENHEIMER

Montgomery, H., Horwitz, O., Peirce, G., and Sayen, A.: Experimental Immersion Foot. I. The Effects of Prolonged Exposure to Water at 3 C. on the Oxygen Tension and Temperature of the Rabbit Leg. J. Clin. Investigation **33:** 361 (Mar.), 1954.

By use of the platinum electrode method for estimating oxygen tension in tissues, it was found that the temperatures of muscle and subcutaneous spaces decreased to levels characteristic of markedly reduced blood flows when the animal's legs were exposed to water at 3 C. The oxygen tension of the tissues was usually depressed by cold, showing a tendency to a greater reduction in supply of oxygen than in utilization. An interesting observation was that when the animals were given oxygen by inhalation, the tension of oxygen in the cold tissues rose to or above the level prior to immersion in the cold water.

WAIFE

Horwitz, O., Montgomery, H., Sayen, A., and Mescon, H.: Experimental Immersion Foot. II. Functional and Histological Changes in the Rabbit Leg Exposed to Water at 3 C., and Therapeutic Trial of Cortisone and of Inhaled Oxygen. J. Clin. Investigation **33:** 370 (Mar.), 1954.

The hind legs of rabbits were immersed in cold water for times varying from 8 to 64 hours. With the development of "immersion foot," there developed an inability to spread toes, to dorsiflex the foot, to hop normally, or to bear weight. In the muscles, certain pathologic changes were noted. These included cellular infiltration, fragmentation, and abnormal variation in the size of the muscle bundles, together with tissue edema. The degree of alteration, both of histologic and functional nature, varied directly with the duration of exposure. However, an abrupt increase in the changes developed after 30 hours.

Although oxygen breathing did not modify the pathologic changes in the muscle, there was some evidence that administration of oxygen during exposure suppressed the functional alterations when oxygen was inhaled throughout a 30-hour exposure.

No beneficial effect from cortisone was demonstrated.

WAIFE

Hellman, L., Rosenfeld, R. S., and Gallagher, T. S.: Cholesterol Synthesis from C^{14}-Acetate in Man. J. Clin. Investigation **33:** 149 (Feb.), 1954.

Six patients with carcinoma and a limited life expectancy received about 200 microcuries of C^{14} administered as acetate-2-C^{14}. Free and ester cholesterol of plasma were determined at periodic intervals. From specific activity curves, it was shown that the formation of labeled free cholesterol preceded that of the esterified form. This suggests that ester cholesterol is synthesized from the labeled free sterol. From the curves obtained, the authors conclude that there is no equilibrium between the ester and free cholesterol fractions. Ester cholesterol, once formed from the free sterol, may not be reversibly hydrolyzed back to the free form. Two days are required for the specific activity of the ester to come into equilibrium with that of the free sterol. This lag period is a function of the time required for esterification of newly formed free cholesterol. Because many distribution and metabolic reactions of cholesterol are reflected in the disappearance curve, no conclusion can be drawn about the plasma turnover of cholesterol until additional information is available. It is also not known whether the data reported from these patients with cancer would necessarily apply to normal subjects.

WAIFE

Wayne, H. H., Weir, A. F., Jr., Barnes, J. A., Joyner, J. T., III, Tuttle, D., Lide, T. and Green, H. D.: Interrelationship of Liver Perfusion, Bacteremia and VDM in Hemorrhagic Hypotensive Shock. Am. J. Physiol. **176:** 301 (Feb.), 1954.

In an animal in shock, arterial perfusion of the liver from a normotensive donor delays the fatal outcome. Even autoperfusion is of some value. Inhibition of bacterial growth did not seem to be responsible for the effects of arterial perfusion. VDM and VEM were found only in a few cases, and there was no correlation with the shock state when they were present.

OPPENHEIMER

Robard, S., Reyes, M., Mininni, G., and Saiki, H.: Neurohumoral Transmission of the Pressor Response to Intracranial Compression. Am. J. Physiol. **176:** 341 (Feb.), 1954.

The test objects were chicks and rabbits. After a delay, an acute rise in intracranial pressure produces a pressor response. This delay seems to be related to the circulation rate since hypothermia increases the delay and the circulation time about equally. Response to an increase in intracranial pressure apparently involves medulla and sympathetic chains. The authors are of the opinion that graded amounts of a pressor material may be released into venous capillaries. This material resembles norepinephrine and acts on systemic arterioles after complete circulation. This pressor substance is blocked by Dibenamine and Benzodioxane. In a few cases, the pressor effect was reversed, especially by Benzodioxane. Tetraethylammonium did not block the response. The pressor material apparently arises outside the adrenal gland and other abdominal viscera.

OPPENHEIMER

Loyke, H. F., and Hoobler, S. W.: Effect of Splanchnicectomy on the Hypoglycemia and Eosinopenic Response to Insulin. Am. J. M. Sc. **227:** 304 (March), 1954.

Insulin-induced hypoglycemia is known to evoke the release of epinephrine in the presence of intact sympathetic innervation in animals. The epinephrine response to hypoglycemia in the present study was measured by the occurrence of eosinopenia. Observations on normotensive and hypertensive patients revealed comparable responses in the eosinopenic index. In the immediate postoperative period, the hypertensive patients were resistant to insulin hypoglycemia and showed no eosinopenia. In the patients who had undergone splanchnicectomy one or more years previously, two types of responses were noted. The patients with "good" surgical results failed to develop eosinopenia during hypoglycemia while those with "poor" results manifested the usual eosinopenia during hypoglycemia. However, the adrenal cortical responses in the "good" cases were found to be normal. It is suggested that the patients with a satisfactory surgical result have had an effective denervation of the adrenal medulla since the reflex release of epinephrine by hypoglycemia is absent in this group. The decreased nervousness, weight gain and reduced metabolic rate after sympathectomy are in accord with this explanation.

SHUMAN

Holland, W. C., Greig, M. E., and Dunn, C. E.: Factors Affecting the Action of Lanatoside C on the Potassium Content of Isolated Perfused Guinea Pig Hearts. Am. J. Physiol. **176:** 227 (Feb.), 1954.

Concentrations of lanatoside C which depress S-T segments and T waves produce arrhythmias and disturbances in conduction; they also cause a loss of potassium from heart muscle and decrease cholinesterase activity. Potassium and acetylcholine present in the medium monitor the effect of the glycoside. High potassium and acetylcholine levels decrease glycoside effects while low potassium increases it. T-wave depression may depend on glycoside inhibition of cholinesterase activity.

OPPENHEIMER

Eastham, R. D.: The Serum Viscosity and the Serum Proteins. J. Clin. Path. **7:** 66 (Feb.), 1954.

The author investigated the possibility of estimating the albumin-globulin ratio of the serum from the total protein content (specific gravity method) and the viscosity. If this method were feasible, it would be possible to make such estimations in less than 15 minutes per serum.

In general, it was found that although the serum viscosity rose as the albumin-globulin ratio fell, there was a wide scatter in the albumin-globulin ratio readings at any given viscosity value. The degree of scatter was sufficient to make the method unreliable. The lack of correlation is probably due to the different effects of the various globulin fractions on the serum viscosity, and also to the possibility that some of these fractions are heterogeneous.

ENSELBERG

White, A. G., Kurtz, M., and Rubin, G.: Comparative Renal Responses to Water and the Antidiuretic Hormone in Diabetes Insipidus and in Chronic Renal Disease. Am. J. Med. **16:** 220 (Feb.), 1954.

Polyuria with inability to concentrate the urine in chronic nephritis corresponds, within the limitations of the impaired glomerular filtration rate, to the manifestations of diabetes insipidus. The authors suggest that inability of the renal tubular end-organ to respond to the antidiuretic hormone, due to renal disease, may result in loss of water in much the same way as in primary deficiency of antidiuretic hormone secretion. This interesting thesis is supported by comparative measurements of water diuresis and antidiuresis in four patients with diabetes insipidus and five patients with chronic renal disease. Following oral hydration (1500 cc. within 30 minutes), the patients with renal disease showed impairment of water diuresis, as demonstrated by lack of attainment of a normal peak diuresis and excretion of a subnormal quantity of water during the five-hour period of observation. During intravenous hydration with 5 per cent glucose in water at 10 cc. per minute, both groups of patients showed prompt attainment of a plateau of urine flow in contrast to the normal curve which reaches a peak at approximately 85 minutes under the same experimental conditions. The patients

with renal disease tended to excrete an even higher proportion of the filtered water load than did those with diabetes insipidus. Both groups of patients demonstrated subnormal antidiuresis following the intravenous administration of 0.57 mU. per kilogram of pitressin during continuous intravenous hydration with 5 per cent glucose in water (10 cc. per minute). The only other observed disturbance in either serum or urinary electrolytes during the hydration or antidiuresis (pitressin) experiments was a tendency for the concentration of sodium in the serum to decrease following administration of pitressin to patients with renal disease.

HARRIS

PATHOLOGY

Hegglin, R., and Zollinger, H.: A Case of Pulmonary Sclerosis of Particular Etiology. (Scar Tissue of the Mediastinum). Cardiologia **24:** 92 (Fasc. 2), 1954.

A 30 year old man with chronic pulmonary disease and pulmonary hypertension was considered, on the basis of the history and the physical and laboratory findings, to exhibit a rare instance of primary pulmonary sclerosis. The patient died in progressive heart failure, and autopsy revealed marked sclerosis of large and small pulmonary vessels. However, this was secondary to severe scarring of mediastinal structures. Dense fibrotic tissue encapsulated and compressed all pulmonary veins and also partially affected the pulmonary arteries. The peripheral vessels were free from arteriosclerosis.

This case shows that the role of metabolic factors, particularly a disturbance of lipid metabolism, is, at the present, overestimated as the principal etiologic factor in the pathogenesis of arteriosclerosis. Mechanical factors leading to local obstruction of the circulation may be more important than generally conceded in the development of vascular sclerosis, as demonstrated in this instance.

PICK

Rossi, E.: Endocardial Fibroelastosis. Cardiologia **24:** 115 (Fasc. 2), 1954.

Clinical and anatomic aspects of endocardial sclerosis (fibroelastosis) are described on the basis of 12 personal observations by the author. From the clinical standpoint, three types can be distinguished. The first, a fulminating variety, has a rapidly fatal course with dyspnea, cyanosis and heart failure. It occurs in infants less than 6 weeks of age and represents about one-fourth of all cases. The second "acute" type, is observed in about half of the cases at an age between 6 weeks and 6 months and is characterized by a paroxysmal form of dyspnea and cyanosis, initiated by attacks of cough and restlessness. The third type shows a chronic evolution of the above signs in association with malnutrition.

Roentgenologically, the heart is enlarged with an ovoid contour caused by dilatation of the left chambers. The electrocardiogram characteristically reveals the adult pattern of left heart strain. Angiocardiographic findings are not typical except for the slow emptying of the left ventricle so that the aortic shadow is poorly outlined.

Anatomically, the heart is considerably enlarged, weighing up to five times the normal, and the endocardial layer is thickened up to 30 times the normal. Usually the lesion is confined to the left ventricle and may affect the valves. The prognosis is very poor though some favorable results have been reported in cases treated by cortisone.

PICK

Shimkin, M. B., and Burnett, R. C.: Secondary Neoplasms of the Heart. Arch. Int. Med. **93:** 205 (Feb.), 1954.

Fifty-three cases of secondary involvement of the heart by neoplasm are reported from a total of 288 necropsies on patients with neoplastic disease. These cases are reviewed as to their frequency, distribution and clinical and pathologic characteristics. It was found that 14 per cent of patients with carcinoma and sarcoma and 25 per cent of patients with leukemias had cardiac metastases or involvement. Although a definite antemortem diagnosis of metastasis to the heart was made in only two patients, various signs and symptoms that in retrospect point attention to cardiac involvement were present in 50 per cent of the cases. Variable but abnormal electrocardiograms were found in 23 of 32 patients. The findings are compared with other series in the literature and their possible significance is discussed.

BERNSTEIN

PHARMACOLOGY

Scurr, C. F.: Controlled Hypotension with Arfonad. Lancet **6806:** 338 (Feb. 13), 1954.

Arfonad is preferable to methonium compounds for inducing hypotension for surgical purposes. Since the effects are evanescent they are readily controlled by discontinuing administration of the drug. The use of Arfonad does not, however, remove the inherent dangers of severe arterial hypotension.

BERNSTEIN

Kilduff, C. J.: The Use of Arfonad in Controlled Hypotension. Lancet, **6806:** 325 (Feb. 13), 1954.

Arfonad has been used to obtain a dry operating field in 50 surgical operations on the head, neck, and chest wall by an induced hypotension. The new single-dose technic of administration is described. With this technic the total dosage of Arfonad used has always been less than that required when the drug is given by intravenous infusion. No undesirable effects have been noticed. With Arfonad it is possible to exercise close control over the blood-

pressure, and the drug is particularly useful when only a short period of hypotension is required.

BERNSTEIN

Lavenne, F., Tyberghein, J., and Sonnet, J.: The The Action of Procaine Amide in the Wolff-Parkinson-White Syndrome. Acta cardiol. **8:** 384, 1953.

The action of procaine amide in the Wolff-Parkinson-White syndrome was studied in four cases. In two of them, the drug had no effect. In a third case, the electrocardiographic diagnosis was that of Wenckebach periods, Wolff-Parkinson-White syndrome, and premature beats with a Wolff-Parkinson-White configuration. Oral administration of the drug was followed on one occasion by gradual increase of the P-Q interval and decrease of QRS duration. On another occasion, the electrocardiogram showed premature beats with a Wolff-Parkinson-White configuration, followed by compensatory pause, and QRS complexes with normal P-Q intervals and normal duration and configuration. After procaine amide, the premature beats disappeared and all the QRS complexes were normal, in spite of the fact that the rate remained slow.

In the fourth case with the Wolff-Parkinson-White syndrome, atropine and exertion had no effect. Procaine amide was administered either by mouth or by intravenous injection, but had only a temporary effect.

The authors point out the different response of these cases to procaine amide. They state that the gradual disappearance of the electrocardiographic signs is against the theory of the accessory bundle and may be explained by an ectopic ventricular center. The presence of premature beats with Wolff-Parkinson-White configuration, as in one of the cases, supports the idea that procaine amide decreases the excitability of the ectopic ventricular center. On the other hand, if procaine amide has no effect, it might be admitted that the Wolff-Parkinson-White configuration is not due to an ectopic focus.

The authors underline the utility of procaine amide in differentiating the various types of Wolff-Parkinson-White syndrome.

LUISADA

Goodman, E. L., and Housel, E. L.: The Effect of d-Amphetamine Sulphate in the Treatment of the Obese Hypertensive Patient. Am. J. M. Sc. **227:** 250 (March), 1954.

The effects of oral and intravenously administered *d*-amphetamine upon the blood pressure, heart rate and peripheral circulation in obese hypertensive subjects were studied. Fourteen patients took the drug orally over an average period of 152 days without any increase in blood pressure above the fluctuations observed prior to the onset of the study. Although an anorexogenic effect was noted in each instance, changes in body weight were inconstant varying from a gain of 10 pounds to a loss of 10 pounds. Intravenous administration resulted in a slight rise in blood pressure in most instances and a moderate peripheral vasoconstriction, the latter being detected by the use of plethysmography. A decrease in skin temperature was observed in 5 of 13 patients. There were no side effects noted following intravenous administration of the drug. The authors conclude that *d*-amphetamine consistently reduces the appetite but that weight loss does not occur without dietary restriction.

SHUMAN

Moyer, J. H., Kent, B., Knight, R., Morris, G., Huggins, R., and Handley, C. A.: Laboratory and Clinical Observations on Chlorpromazine (SKF-2601-A)-Hemodynamics and Toxicological Studies. Am. J. M. Sc. **227:** 283 (Mar.), 1954.

Cardiovascular and renal hemodynamic studies were conducted on animals following administration of Chlorpromazine. Clinical observations were made on 38 control subjects and 25 patients with nausea and vomiting receiving the drug. A hypotensive effect was observed in many instances due to a decrease in peripheral resistance with a variable effect upon the cardiac output. Initially, cardiac output may show an increase but with larger doses the blood pressure decreased and cardiac output was reduced. Parenteral administration appeared to increase sodium and water excretions. The clinical observations revealed no evidence of hepatic or renal toxicity. However, in several patients with hepatic disease the response to the drug was intensified and a sedative effect was noted possibly as a result of decreased destruction of the agent by the liver. Alterations of the electrocardiogram were noted in two patients in whom the changes could have been attributed to the underlying disease.

SHUMAN

Brodie, B. B., Lowman, E. W., Burns, J. J., Lee, P. R., Chenkin, T., Goldman, A., Weiner, M., and Steele, J. M.: Observations on the Antirheumatic and Physiologic Effects of Phenylbutazone (Butazolidin) and Some Comparisons with Cortisone. Am. J. Med. **16:** 181 (Feb.), 1954.

Phenylbutazone exerts antirheumatic effects in patients with rheumatoid arthritis which are comparable to those shown by cortisone and corticotropin. The drug causes urinary retention of sodium, chloride and water, and may reactivate peptic ulcers. Unlike cortisone it does not affect the excretion of potassium nor does it cause eosinopenia or increased ketosteroid excretion. It is concluded that the action of phenylbutazone is not mediated, directly or indirectly, through the adrenal cortex. During phenylbutazone therapy there is often a fall in red-cell count, hemoglobin and hematocrit which is primarily the result of hemodilution and

not of depression of the hematopoietic system. Plasma levels approach a limiting concentration as dosage is increased. This limiting concentration varies widely from patient to patient. Most subjects achieve plasma levels on 400 to 600 mg. daily that are only slightly lower than when 800 mg. are given. In an over-all series of 87 patients treated with phenylbutazone for protracted periods, undesirable drug effects necessitated discontinuance of therapy in 20 per cent of cases. This was not, however, due to bone marrow depression.

HARRIS

Friedman, M., St. George, S., and Bine, R.: The Behavior and Fate of Digitoxin in the Experimental Animal and Man. Med. **33:** 15 (Feb.), 1954.

The authors review the methods of assay of digitoxin, chemical, radioisotope, and bioassay, and describe their method which employs the embryo duck heart. The available evidence, including the author's, indicates that orally administered digitoxin is completely absorbed in the experimental animal and man. In man, absorption does not appear to be impaired by heart failure. After oral ingestion the blood concentration of the glycoside is too low to be detectable, regardless of the size of the dose. This is probably due to the slow rate of intestinal absorption.

Digitoxin in the blood is physically bound to albumin by absorption, though there is some dissociation discernible in in vitro preparations. The glycoside concentration in human blood falls by half in the first three minutes after intravenous injection of 1.2 mg. However, one hour later the concentration is barely decreased further. At the end of three hours, no detectable digitoxin remains in the blood. On the other hand, a similar dose of lanatoside C disappears from the blood within 30 minutes. This is attributed to the fact that lanatoside C is not bound to plasma albumin.

Digitoxin is deposited in various tissues as well as the heart. Indeed, animal studies show that the liver or the kidney may contain more glycoside per gram than the heart. The rate of disappearance of digitoxin from the heart is as rapid as from other tissues, and may even be faster than from the kidneys, liver or brain in some animals. The authors paid special attention to the question of the penetration of digitoxin into extravascular fluid. They were unable to find more than traces in the extravascular fluids of the peritoneal and pleural cavities or subcutaneous tissues of cardiac and noncardiac patients. This finding indicates that the phenomenon of digitalis intoxication, following the rapid reabsorption of collections of edema fluid, results from causes other than the recirculation of digitalis.

The basic mechanisms involved in the action of digitalis on the heart are unknown, and it appears that the drug does not alter the energy forming reactions of the failing heart. However, there is evidence which implies that the mode of action is to improve a diminished response of the failing contractile mass to an undiminished supply of chemical energy, thereby improving mechanical efficiency.

A small part of injected digitoxin is excreted in the bile of laboratory animals and man. Except for the frog, no laboratory animal excretes a significant amount of the drug in the urine. On the other hand, man can excrete considerable quantities in the urine. As much as 50 per cent of a single dose can be so excreted, though it may take several days to do it. Normal subjects and patients in acute left ventricular failure excrete about 40 per cent of the daily dose, after initial digitalization with 1.2 mg. and maintenance doses of 0.1 mg. a day. Patients with right ventricular failure have a similar excretory rate following initial decreased excretion the first 24 hours after taking the drug. In all groups, overdigitalization results in renal excretion of the drug in much larger amounts. Man also differs from other species in that he has the ability to destroy digitoxin in quantities up to 50 μg. a day, whereas the evidence for destruction in animals is not too satisfactory for some species.

ENSELBERG

Singer, R. B.: The Acid-base Disturbance in Salicylate Intoxication. Medicine **33:** 1 (Feb.), 1954.

The hyperpnea of salicylate intoxication is associated with a decrease in plasma carbon dioxide concentration and usually a decrease in the carbon dioxide combining power. The cause of the lowered carbon dioxide content has been attributed by some investigators to respiratory alkalosis, and by others to metabolic acidosis. Because of the conflicting interpretations, the author re-examined the cases reported in the literature, and investigated others in which determinations included whole blood carbon dioxide and pH.

The data indicate that the acid-base disturbance is at first a carbon dioxide deficit, or respiratory alkalosis, which goes on in severe cases to a mixed disturbance in which a primary alkali or buffer base deficit is added (metabolic acidosis). It is therefore emphasized that the diagnosis cannot be simply made on the basis of carbon dioxide concentration alone. Since carbon dioxide concentration is lowered in respiratory alkalosis and in metabolic acidosis, and since hyperventilation is present in both conditions, a blood pH is essential. When the plasma carbon dioxide is below 7 mM. per liter, there is usually an acid pH regardless of the degree of hyperventilation. Except for this, no conclusion can be drawn from the carbon dioxide content regarding the pH. Even less reliable is the determination of the carbon dioxide combining power, especially during severe hyperventilation when it

will lead the clinician to underestimate the severity of the acid-base disturbance. Hyperventilation and respiratory alkalosis are due to a specific action of salicylates in stimulating the nervous control of respiration which results in a primary increase of depth of breathing. This may be followed by extremely low carbon dioxide pressures. Another direct effect of salicylate is probably upon intermediary cellular metabolism, resulting in accumulation of organic acid metabolites.

ENSELBERG

Dunster, M. O., McGowan, G. K., and Bennett, D.: The Effect of Cation Exchange Resins in the Treatment of Pre-eclamptic Toxemia of Pregnancy. J. Obst. & Gynec. Brit. Emp. **61:** 31 (Feb.), 1954.

The authors present seven cases of pre-eclamptic toxemia of pregnancy in whom a cation exchange resin (Resodec) was added to the therapy after maximal beneficial effect had been obtained with a regimen of bed rest in the hospital, sedation, and a 0.8 Gm. low sodium diet. Plasma electrolyte determinations were made. The results indicated that cation exchange resins were effective agents in reversing fluid retention in this condition by diminishing the intestinal absorption of sodium when combined with a low sodium diet. They also produced an acidosis which initially promoted further sodium loss by increasing the renal excretion. The degree of acidosis was not severe and could be reversed by the simultaneous administration of an anion exchange resin. Severe depletion of calcium, sodium, and potassium were not found during short courses of treatment. The resin therapy produced an improvement in the reduction of blood pressure and a distinct fall in the urinary protein excretion as well as a loss of edema fluid. This would indicate that the resin may have improved the underlying toxemic condition. As far as could be determined, the resin had no ill-effect on the fetus. Of the three babies that were lost in this series, one was hydrocephalic and the other two died of prematurity. The authors conclude that the cation exchange resin is the most effective available agent for controlling excessive fluid retention in the pre-eclamptic state and that it improves the condition by increasing renal function. The prolonged use of resin therapy, however, should be restricted to the cases where it is decided to prolong pregnancy for a few more weeks in the interests of the fetus.

SAGALL

Fourman, P.: Depletion of Potassium Induced in Man With an Exchange Resin. Clin. Sc. **13:** 93 (Feb.), 1954.

Metabolic studies were performed on two normal subjects who were depleted of potassium by the use of a cation-exchange resin while on a potassium deficient diet. On two occasions the potassium loss amounted to 670 and 840 mEq., about 28 per cent of the total body potassium of the subjects. Proportionally less water and phosphate were lost from the cells than potassium, and during the administration of resin neither sodium, magnesium nor calcium were retained in place of potassium. The potassium loss was accompanied by extracellular acidosis.

After the resin was stopped, the potassium deficiency was not restored because of the inadequate diet. However, more sodium was available and was retained in excess at first intracellularly and later extracellularly to produce edema. Also, during recovery, the extracellular acidosis was succeeded by mild alkalosis. During these experiments the subjects experienced mental confusion, weakness and anorexia, especially during the acidosis.

ENSELBERG

Deming, Q. B., and Gerbode, F.: Salt Administration After Mitral Valvotomy. Ann. Surg. **139:** 143 (Feb.), 1954.

The authors pointed out that complete elimination of salt intake after mitral surgery may be dangerous, particularly if the patient was previously made to lose salt and water through intensive diuretic therapy. It was their opinion that an intake of 3 Gm. of sodium chloride per day would meet the demands of the body for sodium and at the same time this quantity would not be large enough to do harm. On such a regimen, pulmonary edema was not noted in any of their patients, while serious hyponatremia was avoided.

ABRAMSON

PHYSICAL SIGNS

Giges, B., and Kunkel, H. G.: Osmotic Pressure Measurements of Serum and Ascitic Fluid in Patients with Cirrhosis of the Liver. J. Clin. Investigation **33:** 257 (Feb.), 1954.

One of the factors commonly considered in a position of importance in the formation of ascites is the osmotic pressure of the serum. In this study, osmotic pressure measurements were made on serum and ascitic fluids from 46 patients with various types of liver disease. The subjects were on a low sodium diet and were neither increasing nor decreasing the amount of ascites. A Hepp osmometer was used for the determinations.

Ascites appeared to be associated with osmotic levels ranging from the low value of 148 mm. of water to the high value of 418 mm. of water. Higher levels of osmotic pressure were found in patients with the alcoholic and nutritional type of cirrhosis, whereas in other types ascites appeared to be more directly related to a critical serum osmotic pressure level. Values below 260 mm. of water were uniformly associated with ascites.

The authors also discuss the limitations of the application of measurements of the "effective portal

pressure" which is taken to be the difference between the serum osmotic pressure and the ascitic osmotic pressure. In some instances the serum osmotic pressure was relatively too low to give an accurate measurement.

The authors conclude that Starling's hypothesis remains of great value in describing the equilibrium conditions and in accounting for the respective protein concentrations of serum and ascitic fluid.

WAIFE

Lloyd, C. W., Loewy, E., Pierog, S., Bradwick, K., and Sostheim, R.: Presence of Antidiuretic Material in Blood of Hypophysectomized Rats. Proc. Soc. Exper. Biol. Med. **85**: 333 (Feb.), 1954.

By well recognized biologic methods for assaying antidiuretic hormone in serum or plasma, the authors showed that in recently hypophysectomized rats no antidiuretic hormone could be found in serum. In more remote hypophysectomized rats, detectable amounts of antidiuretic hormone equivalent to 60 to 400 microunits of pitressin per cc. serum were found. The hypothalamic nuclei of seven animals, hypophysectomized longer than 30 days, contained activity equivalent to 5 milliunits or more of pitressin. It is suggested that in the hypophysectomized animal the hypothalamus is capable of storing and secreting antidiuretic hormone.

HARVEY

Nazzi, V., and Morassuti, P.: The Esophageal Tracing in Mitral Valve Disease. Cuore e Circolaz. **37**: 271, 1953.

The authors present a detailed study of esophageal tracings in normal subjects and cardiac patients. They studied both the pressure tracings and the plain atriograms. The authors discuss the more important applications of this method in the diagnosis of mitral regurgitation. Because of the complexity of the data, one should read the original paper for the technical details.

The normal pattern of the esophageal tracings may be altered by variations of atrial and ventricular activity, variations of the anatomic position of the heart, respiratory movements, or changes in the arterial and venous blood pressure.

The physiologic esophageal tracing is described. Its pattern is found similar to that of the phlebogram. The changes of the tracing in mitral regurgitation, mitral stenosis, and combined defects are discussed.

Both the esophagocardiogram and the esophageal pressure tracing are useful in cardiology because they give information about the hemodynamics of the heart and help to indicate suitable cases for mitral commissurotomy.

LUISADA

RHEUMATIC FEVER

Perry, H. M., and Schroeder, H. A.: Syndrome Simulating Collagen Disease Caused by Hydralazine (Apresoline). J. A. M. A. **154**: 670 (Feb. 20), 1954.

Hydralazine (Apresoline) hydrochloride is a highly reactive compound that combines with carbonyl and sulfhydril radicals and has a strong affinity for certain heavy metal ions. Late reactions to this agent were predicted and these have taken the form of collagen disease in all stages of severity. One case of pancytopenia has been reported. In 211 patients given hydralazine hydrochloride continuously for 2 to 22 months, 17 developed collagen disease of various degrees of severity. The causitive role of the drug in this syndrome is substantiated by the following facts. (1) Symptoms and signs regressed rapidly when the drug was omitted. (2) In five cases one or two doses of the drug caused high fever and acute recurrence of joint symptoms. (3) Chemical analogs of hydralazine caused the same signs and symptoms that hydralazine thrice produced. (4) The disease became severer (disseminated lupus erythematosus) when administration was continued despite symptoms. Regression occurred when the drug was discontinued. (5) The incidence of the syndrome has increased rapidly in the past year. It is pointed out that certain tests, usually correlated with hepatic function, are helpful diagnostic aids.

KITCHELL

Wallach, J. B., Lukash, L., and Angrist, A. A.: Source of Emboli in Rheumatic Heart Disease. Am. J. Clin. Path. **24**: 172 (Feb.), 1954.

The role nonbacterial thrombotic endocarditis played as a source for visceral emboli in 509 autopsied cases of rheumatic heart disease is studied. In these hearts thrombi were in the left chambers of 123, nonbacterial vegetations on the left sided valves in 152, and bacterial vegetations on the left sided valves in 65. There were 113 cases in whom there were cerebral, splenic, or renal infarctions. In 45 cases no source for emboli could be found; in 23, only nonbacterial thrombotic vegatations were found; in 49, only thrombi in the left chambers were found; and in 19, thrombi in the left chambers and nonbacterial vegatations together were found. The authors feel that, contrary to other reports, nonbacterial thrombotic endocarditis is an important source of visceral emboli in patients with rheumatic heart disease.

HARVEY

Houser, H. B., Clark, E. J., and Stolzer, B. L.: Comparative Effects of Aspirin, ACTH, and Cortisone on the Course of Rheumatic Fever in Young Adult Males. Am. J. Med. **16**: 168 (Feb.), 1954.

A comparison of the effects of treatment with aspirin, cortisone and corticotropin in 148 young adult males with acute rheumatic fever indicates that aspirin relieved fever, joint pain and objective evidences of joint involvement most promptly. Corticotropin was more effective in this respect than cortisone. Except for the promptness of relief these three drugs showed little difference in their effects on the symptoms of acute rheumatic fever. The pattern of response of the erythrocyte sedimentation rate was different in each of the three therapy groups. Cortisone and corticotropin resulted in shortening the duration of abnormal auriculoventricular conduction. In each group new murmurs appeared and persisted while the patients were receiving ostensibly full therapeutic dosages of the drugs. The final interpretation of the effects of these drugs on carditis must await the results of a long-term follow-up. A clinical and/or laboratory relapse or "rebound" occurred in almost all of the patients in each group after cessation of therapy. This relapse subsided spontaneously in all except six aspirin-treated patients, one cortisone-treated patient and one corticotropin-treated patients. Toxicity and/or side-effects associated with use of the three drugs occurred in all the aspirin and corticotropin-treated patients and in 75 per cent of the cortisone-treated patients. Acute psychoses developed in two corticotropin-treated patients. It is clear that the over-all effect of each of the drugs leaves much to be desired in the treatment of acute rheumatic fever and that adequate therapy for this disease is not presently available.

HARRIS

Gray, F. D., and Gray, F. G.: The Effect of Lanatoside C on the Circulatory and Ventilatory Changes of Chronic Rheumatic Heart Disease with Mitral Stenosis. Am. Heart J. **47**: 282 (Feb.), 1954.

Circulatory and ventilatory studies were performed on six patients with chronic rheumatic heart disease and mitral stenosis before and one hour after the administration of an effective intravenous dose of lanatoside C. Pulmonary function studies were done the day before and again the day after digitalization. These consisted of subdivisions of lung volumes and maximal breathing capacity recorded on a 9 liter, bell-type respirometer, and functional residual capacity. Other data collected included blood gas and shunt data, blood flow data and valve areas, blood pressure and resistance data. Clinical improvement after digitalization was noted in only three of the six patients. Lanatoside C consistently increased the work of the heart by increasing the right ventricular and peripheral arterial pressures and, in all but one of the six patients, the rate of systemic blood flow. The increased work of the heart seen after lanatoside C in some patients who had neither frank signs of congestive failure nor a clean cut clinical response to full digitalization was cited as evidence supporting the early use of digitalis in patients with mitral stenosis. In the presence of multiple valve lesions, a rise in the rate of systemic blood flow after digitalization was suggested as a necessary criterion in the selection of patients for mitral valvulotomy.

RINZLER

Edström, G., and Gedda, P. O.: Investigation in the Localisations and Forms of Some Visceral Anatomical Lesions in Rheumatic Fever. Acta med. scandinav. **147**: 367 (Fasc. 5–6), 1954.

A series of 9,898 autopsies performed at the Pathologico-anatomical Institute of Lund University was reviewed. There were 363 cases showing rheumatic cardiac lesions and in 350 of these death was related directly or indirectly to the rheumatic fever. A history of rheumatic fever was obtained in 200 of the patients. Although the greatest number of deaths occurred during the sixth decade, the average age of death was 48 years. Cardiac lesions were present in all cases and valvular lesions were found in 97 per cent of them. In 27 per cent the valvular lesions were not diagnosed clinically. The mitral valves were involved in 87 per cent of the cases, but there were only 50 cases of pure mitral stenosis (13.8 per cent). Pure aortic lesions were present in 9 per cent and in a single case the involvement was limited to the tricuspid valve. Adhesive pericarditis was present in 28 per cent, but in only two cases was there obstrictive pericarditis and in each of those it was a part of a picture of polyserositis. Six patients showed evidence of diffuse glomerulonephritis and two patients showed evidence of amyloid nephrosis. Death was due to congestive heart failure in 57 per cent, to peripheral embolism in 17 per cent, subacute bacterial endocarditis in 11 per cent and pneumonia in 10 per cent.

ROSENBAUM

ROENTGENOLOGY

Dickerson, R. B.: Performance of Angiocardiography and Cardiac Catheterization as a Combined Procedure. Am. Heart J. **47**: 252 (Feb.), 1954.

The routine use of both angiocardiography and cardiac catheterization as a combined procedure is described. Several cases are reported which seem to illustrate the degree to which the respective findings complement and amplify one another. One particular procedural modification is stressed. This is the use of the bacilic vein high in the arm for the insertion of a polyethylene catheter. Because the dye can be injected close to one heart, less than the usual amount is needed and a dependable visualization of the left heart and aorta by angiocardiography results. Subsequently, the same vein has been used for catheterization, as a part of the same procedure.

RINZLER

SURGERY

Bogardus, G. M., Beretta, F. F., Huff, R. L., and Payne, J. T.: Endarterectomy for Peripheral Arteriosclerosis. Arch. Surg. **68**: 222 (Feb.), 1954.

The authors reviewed the subject of endarterectomy in occlusive arteriosclerotic disease and presented the results obtained in eight patients by use of this method. A detailed study of the lower portion of the aorta and its main subdivisions in cadavers demonstrated the presence of arteriosclerotic plaques on the posterior wall of the lower lumbar aorta in 30 per cent of cases. Histologic examination of involved segments revealed a greatly thickened intima and an irregular, thinned out media.

It was believed that endarterectomy was indicated when the following conditions existed: persistent symptoms of localized arterial insufficiency, the presence of an involved vessel of sufficiently large caliber, and an obstruction which was not of great length. Aortography was considered of value in the proper choice of patients.

The authors were of the opinion that endarterectomy is a feasible and appropriate form of therapy in a small percentage of patients suffering from occlusive arteriosclerotic peripheral vascular disease. The procedure is essentially an intimectomy of thickened, sclerotic and even calcified intima.

ABRAMSON

Szilaghy, D. E., and Hemmer, J. A.: Resection of Aortic Bifurcation and Replacement with Homologous Graft for Aneurysm. J.A.M.A. **154**: 751 (Feb. 27), 1954.

Resection of the aortic bifurcation and grafting is a recent addition to treatment of abdominal aortic aneurysms. The authors add a fifth successful case to the known records. One unsuccessful case has been reported also (total of six operated cases). This replacement of the aortic bifurcation by a homologous graft is still in excellent condition after eight months of observation.

KITCHELL

Ivins, J. C.: The Direct Surgical Treatment of Occlusive Arterial Disease of the Legs. Proc. Staff Meet., Mayo Clin. **29**: 145 (Mar.), 1954.

Occasionally, perhaps once in several hundred cases, a patient with arteriosclerosis obliterans is seen who has intermittent claudication with absent pedal pulses, but who does not have other signs of ischemia. Such a condition generally denotes segmental obstruction. Rest pain and other signs of severe ischemia are absent because collateral vessels can re-enter the main channel distal to the obstruction, but claudication occurs because these collateral vessels will not carry enough increased blood flow to nourish the limb during exercises. If, in such a case, the arteriogram shows a segmental obstruction with a fairly normal-appearing artery above and below, two surgical procedures can be considered. These are excision of the occluded segment, with use of a vein graft to re-establish continuity of the vessel, or endarterectomy in which the vessel is opened, the area of atheromatosis and thrombosis is removed and the arterial wall is repaired by suture of the adventitia and remaining media.

There are no long-term follow-up studies to permit assessment of the value of these procedures. The decision as to whether a vein graft will be used, or endarterectomy performed, generally is made after the vessel has been surgically exposed and examined.

SIMON

Zeavin, I., Virtue, R. W., and Swan, H.: Cessation of Circulation in General Hypothermia. II. Anesthetic Management. Anesthesiology **15**: 113 (Mar.), 1954.

The authors review the historical aspects of hypothermia as a sedative and as an anesthetic agent particularly for cardiac operations. The basic changes occurring in the dog during hypothermia are described. Below 21 C. ventricular fibrillation was a frequent problem. The mortality due to ventricular fibrillation was reduced to 8 per cent by the administration of 100 per cent oxygen through an endotracheal tube with rapid ventilation. With the same procedure but allowing the accumulation of carbon dioxide the mortality rose to 50 per cent. In the cold dog the electric defibrillator was not of value, but the administration of potassium chloride was of value in defibrillating the ventricles. The results in the employment of hypothermia in 11 humans are reported. The patients were immersed in ice water after lower second plane ether anesthesia had been induced. Spontaneous respirations usually ceased about 29 C. and hyperventilation thereafter was utilized. After removal from the ice bath the patient's temperature continued to drop for a while. Anesthesia could be maintained without administration of much of the agent. When the patient began to move after body temperature had risen, 50 per cent nitrous oxide in oxygen was employed. In one case ventricular fibrillation occured during the five-minute interval between removal from ice and connection of the electrocardiograph machine. Massage was started two minutes after the onset of ventricular fibrillation and potassium chloride was instilled intraarterially. The patient recovered.

The authors conclude that hypothermia is an effective anesthetic agent and is indicated when (1) the operating team is prepared to recognize and handle the cardiac arrest of the cold heart; (2) when occlusion of the entire circulation is required to perform intracardiac surgical procedures; (3) when hypotension is desired in poor risk patients; (4) when the oxygen demand of cyanotic patients

should be reduced; and (5) when regional occlusion of the circulation is desired for prolonged periods.

SAGALL

Heinzen, B. R., Dunbar, H. S., and Parsons H.: Thrombosis of the Abdominal Aorta and Iliac Arteries. Ann. Surg. **139:** 148 (Feb.), 1954.

The authors reported on 14 cases of Leriche syndrome treated by several different measures. They found that sympathectomy generally did not relieve the symptoms in the extremities. The most satisfactory results were obtained when the disease process was sufficiently limited to permit thromboendarterectomy or resection of the thrombosed segment and replacement by a venous or arterial graft. Abdominal aortography was considered useful in establishing the existence of the Leriche syndrome.

ABRAMSON

Temesvari, A.: Surgical Treatment of Experimental Myocardial Infarction with Revascularization of Cardiac Muscle. Ztschr. Kreislaufforsch. **43:** 189 (Mar.), 1954.

Experiments on dogs are reported in which a pedunculated flap of pectoral or diaphragmatic muscle was successfully implanted into cardiac muscle. After the method proved feasible it was used to replace an excised area of myocardial infarction produced by ligation of a coronary artery. Histologic examination revealed that striated muscle, if sufficiently supplied by blood vessels, remains viable under such circumstances and fuses with ordinary myocardium without much scar formation. None of the operated animals developed heart failure or anatomic evidence of damage of the surrounding myocardium. Fifteen out of 17 animals survived for 8 to 10 months. In 10, ligation of another coronary artery subsequent to the transplant operation did not lead to development of myocardial infarction.

PICK

Sellors, T. H., Bedford, D. E., and Somerville, W.: Valvotomy in the Treatment of Mitral Stenosis. Brit. M. J. **2:** 1059 (Nov. 14), 1953.

In the opinion of the authors the signs of a pliant diaphragmatic valve type of mitral stenosis (the variety most amenable to valvotomy) are a snapping apex beat, a snapping first sound (closing snap), and a loud opening snap of clicking quality. Additional evidence of severe mitral stenosis is provided by an intense diastolic murmur, a small sustained pulse and a small aorta by x-ray. The surgeon can feel the snapping movement of the mitral valve. They believe cardiac catheterization is not necessary and that an assessment of the state of the right ventricle by physical examination and x-rays is more valuable than an isolated determination of pulmonary artery pressure. Those cases who have become recently incapacitated by paroxysmal pulmonary edema are considered ideal. Mitral valvotomy was performed in 150 patients. The male to female ratio was 1 to 4. Atrial fibrillation was present in 41 per cent. Ages of the patients varied from 19 to 57 years. The immediate (within four days) mortality was 2.7 per cent. Four others died after an interval of one month or more. Of 111 cases who have been followed long enough to permit assessment, good results were achieved in 74 per cent, and fair or poor results in the rest.

MCKUSICK

Langston, K. W.: Controlled Hypotension to Reduce Surgical Hemorrhage. Canad. M.A.J. **69:** 375 (Oct.), 1953.

A preliminary report is made on 35 cases where hexamethonium bromide has been used to produce hypotension during anesthesia. The assessment of results has shown a valuable reduction in blood loss during operation, by accurate measurement, and consequent reduction in operative time. Nevertheless, a note of caution must be emphasized. "Controlled hypotension" demands an adequate preoperative blood volume and the immediate replacement of all blood loss. At all times a patent airway and complete oxygenation are essential, with provision for expert and meticulous postoperative care. The contraindications must be respected, and it is not a technic to be employed by inexperienced or occasional anesthetists. Even in the most skilled hands, controlled hypotension should only be used in the presence of specific and urgent indications.

BERNSTEIN

THROMBOEMBOLIC PHENOMENA

Wegelius, O.: Deep Venous Thrombosis in the Lower Limbs as a Complication of Internal Diseases. Acta. med. Scandinav. **148:** (Fasc. 1), 1954.

A series of 435 patients with some form of thromboembolism observed in the medical departments of the Maria Hospital over a period of six years is reported. This complication occurred in patients with congestive cardiac failure, diseases of the blood, infectious diseases, especially of the respiratory organs, after trauma, and in patients with varices of the legs. In 10 cases there was no obvious cause for the development of thrombosis. Twenty-three per cent of the patients had been at rest in bed during their hospitalization. Twenty-six per cent had been receiving digitalis or mercurial diuretics or both. Studies of the erythrocyte sedimentation rate showed no correlation between erythrocyte aggregation and the occurrence of thromboembolism. Anticoagulant therapy seemed surprisingly ineffective since the rate of pulmonary embolism and the incidence of fatal embolism were broadly similar in the treated and the untreated groups. Of the entire series 25 per cent of the pulmonary complica-

tions and 14.2 per cent of the deaths occurred during anticoagulant therapy making the effectiveness of such treatment doubtful. A comparison of the effectiveness of treatment regulated with the Owren prothrombin percentage method was made with that controlled by the prothrombin index of Quick. This study seemed to indicate that the Owren method was superior.

ROSENBAUM

Paterson, J. C., and McLachlin, J.: Precipitating Factors in Venous Thrombosis. Surg., Gynec. & Obst. **98**: 96 (Jan.), 1954.

On the basis of autopsy material obtained from 165 patients who died of phlebothrombosis, the authors arrived at certain conclusions regarding the etiology of this disorder. They found no evidence to implicate local injury or disease in the vein wall as a cause for intravascular clotting. Furthermore, there was no support for the view that abnormalities in blood coagulation were responsible agents. However, since venous thrombi were found to arise almost invariably in valve pockets, the authors suggested that venous stagnation might be a major factor in the etiology of phlebothrombosis.

ABRAMSON

Shumacker, H. B., Jr., Moore, T. C., and Campbell, J. A.: Functional Venography of the Lower Extremities. Surg., Gynec. & Obst. **98**: 257 (Mar.), 1954.

The authors performed 115 venographic studies on the lower extremities of normal subjects and patients with disturbances of the venous circulation. The injection of the radiopaque material was made into the femoral vein, the popliteal vein, or one of the superficial veins of the thigh, leg or foot. In each instance films were taken before and after exercise.

It was found that regurgitation down the femoral vein following femoral injections or down the deep leg veins following popliteal injections was encountered in a high percentage of both normal and abnormal subjects. Since in all these individuals the deep venous system cleared after exercise, the authors conclude that regurgitation in the deep venous system in quiet dependency is not pathologic. Furthermore, there was no evidence to suggest that abnormal regurgitation occurred in recanalized veins. The clinical implications of such views are stressed.

ABRAMSON

Homans, J.: Thrombosis of the Deep Leg Veins Due to Prolonged Sitting. New England J. Med. **250**: 148 (Jan. 28), 1954.

Five cases are reported of thrombosis of the deep veins of the lower extremities, each instance following a prolonged sitting position. The right leg appears to be more susceptible than the left. The author cautions physicians to be alert to recognize the significance of lameness after airplane flights and automobile trips. This is particularly so in the case of persons over 50 years of age.

ABRAMSON

Popkin, R. J.: Torsion Movements of Arteriosclerotic Cerebral Arteries as a Factor in Transient Cerebral Disturbances. Angiology **5**: 72 (Apr.), 1954.

On purely theoretic grounds, the author attempts to explain some of the acute cerebral episodes, such as aphasia, paresis, and convulsive muscular twitchings, on the basis of a sudden increase in blood volume mechanically distending the cerebral arteries. According to him, in the presence of cerebral arteriosclerosis, this change causes torsion or twisting movements of the diseased segments of vessels, which, in turn, results in an impact against the adjacent brain tissue. The severity of the symptoms depends upon the force, duration and location of the impact.

ABRAMSON

Carter, J. F. B.: Varicose Veins. Lancet **266**: 743 (Apr. 10), 1954.

The authors attempt to assess the results of various methods of treatment of varicose veins in a series of 207 patients. The procedures consisted of injection alone, ligation of the greater saphenous vein and its tributaries, ligation of the greater saphenous vein followed by retrograde injection of a sclerosing solution, interruption of the short saphenous vein in the popliteal space, and stripping and excision. The follow-up period was three years.

It is concluded that complete ablation of the veins by stripping and excision, which was done on 175 limbs, is the most effective measure of those studied.

ABRAMSON

Winsor, T.: Skin Temperatures in Peripheral Vascular Disease. J. A. M. A. **154**: 1404 (Apr. 24), 1954.

The author presents the advantages of the thermistor thermometer over other available clinical instruments for the study of skin temperature in man. He also points out the value of skin temperature readings in certain vascular disorders, in the determination of possible benefits of sympathectomy, in the assessment of relative values of medical therapeutic agents and procedures, and in ascertaining sensitivity to tobacco.

ABRAMSON

Krahl, E., Pratt, G. H., and Rousselot, L. M.: Arterial Angiography in the Diagnosis, Prognosis and Treatment of Occlusive Vascular Disease. Bull. New York Acad. Med. **30**: 122 (Feb.), 1954.

The authors present evidence, using angiography, to show the segmental characteristic of the great majority of the peripheral occlusive arterial diseases. They point out that through accurate study and

interpretation of an arteriogram, much important information regarding prognosis and treatment can be derived.

ABRAMSON

Krahl, E., Pratt, G. H., Rousselot, L. M., and Ruzicka, F. F.: Collateral Circulation in the Arterial Occlusive Disease of the Lower Extremity. Surg., Gynec. & Obst. **98:** 324 (Mar.), 1954.

On the basis of clinical and arteriographic examination of 50 patients with arterial insufficiency of the legs, the authors arrive at certain conclusions regarding collateral circulation. They point out that when the main artery becomes obstructed, the development of a collateral system depends upon five factors: the site of obstruction and length of block, the degree of arteriospasm, the etiology of the arterial disease, the therapeutic measures instituted, and the individual response of the patient.

Various types of vessels appear or develop in response to the stimulus of anoxia. The first consists of areas of hypervascularization, formed by accessory collateral branches, very small in size. Another group is formed of supplemental branches arising either from main or from accessory collateral trunks. These vessels generally run parallel to the obliterated main artery. The third type consists of bridging collaterals which are formed by main collateral branches. These vessels envelop a segmental block of the main artery.

ABRAMSON

Keys, A., Fidanza, F., Scardi, V., Bergami, G., Keys, M. H., and DiLorenzo, F.: Studies on Serum Cholesterol and other Characteristics of Clinically Healthy Men in Naples. Arch. Int. Med. **93:** 328 (Mar.), 1954.

Clinically healthy men, 20 to 55 years old, were studied in Naples, Italy and were compared with findings from Minnesota with regard to diet, serum cholesterol, obesity, and electrocardiographic items. From age 20 to the early thirties the average total cholesterol concentration in the serum of the Italians rose about 3 mg. per 100 ml. annually and corresponded closely with the Minnesotans in this regard and in the absolute concentration at a given age. Thereafter, in sharp contrast with the Minnesotans, the Italians showed no further age trend so that by age 50 there was a mean difference of about 30 mg. per 100 ml. between the population samples.

In the Italians, as in the Minnesotans, when the factor of age was eliminated statistically, there was no important relationship between serum cholesterol concentration and relative obesity as measured by either body weight or skinfold (subcutaneous fat) thickness. Electrocardiographic comparisons showed statistically significant differences between the Italians and the Minnesotans in regard to age trends. The age trend to left axis deviation and prolongation of P-R and diminution of QRS and T potentials, so marked among the Minnesotans, was small or absent among the Italians.

BERNSTEIN

Biegeleisen, H. I.: Hazards of Neglecting Treatment in Varicosis Accompanying Pregnancy. Angiology **5:** 84 (Apr.), 1954.

The author presents the view that during the pregnant state varicosities should be treated using the injection method. It is his belief that surgery is rarely indicated under these circumstances. He emphasizes the point that temporizing is hazardous since the presence of varicosities may increase the tendency to thrombophlebitis.

ABRAMSON

VASCULAR DISEASE

Martin, P.: Phlegmasia Caerulea Dolens. Brit. Med. J. **2:** 1351 (Dec. 19), 1953.

This designation is employed by the author for the association of acute ischemia or even gangrene with thrombophlebitis of an extremity. Pseudoembolic phlebitis, blue phlebitis and gangrenous thrombophlebitis are other terms which have been applied. This particular clinical picture is likely to follow abrupt obstruction of the major venous drainage of a limb. It may follow venous ligation. Heparin, heating of the unaffected extremity, heavy sedation are recommended. Paravertebral sympathetic block may be risky in the presence of heparinization.

McKUSICK

Stern, W. E.: Basilar Artery Aneurysm. Report of a Case Diagnosed Roentgenologically. Am. J. Roentgenol. **71:** 428 (Mar.), 1954.

The author presents a case report of a calcified, globular shaped aneurysm in the prepontine region which occurred in a 59 year old male, causing paralytic and pyramidal tract manifestations. Roentgen diagnosis was established by skull films, laminography and cerebral angiography.

SCHWEDEL

Lathem, W., Lesser, G. T., Messinger, W. J., and Galston, M.: Peripheral Embolism by Metallic Mercury during Arterial Blood Sampling. Arch. Int. Med. **93:** 550 (Apr.), 1954.

Two cases are described in which multiple arterial embolization of the fingers resulted from accidental injection of metallic mercury into the brachial artery during anaerobic blood sampling. No evidence of mercury poisoning appeared in either case. In both, symptoms of circulatory insufficiency of the fingers gradually disappeared, although foreign body abscess formation and elimination of the mercury through the skin continued for a prolonged period. In one case, clubbing of the involved fingers was noted 15 months after the accident and appears to be

permanent. It is recommended that the use of mercury be avoided in the preparation of anaerobic syringes.

BERNSTEIN

Gilfillan, R. W., Jones, O. W. Jr., Roland, S. I., and Wylie, E. J.: Arterial Occlusions Simulating Neurological Disorders of the Lower Limbs. J. A. M. A. **154:** 1149 (Apr. 3), 1954.

Symptoms manifested by patients with pain in the low back and lower extremities due to vascular insufficiency are sufficiently different to separate them clearly from patients with pain secondary to musculoskeletal alteration or nerve root compression. However, there are cases in which patients with atherosclerotic occlusive disease have been subjected to myelography, pneumoencephalography, leg traction, and even laminectomy, because of the similarities in the signs and symptoms. One of the most salient features of arterial occlusive disease is the onset of pain and its rapid increase in close proportion to the amount of muscular exercise of the affected area. Another distinguishing feature is the rapid regression of pain on cessation of the muscular effort that brought it about. The pain of claudication subsides in seconds or minutes, while nerve pressure pain or musculoskeletal disorders aggravated by exercise subside very slowly, and often last hours beyond the aggravating effort. With arterial occlusion there is usually absence of peripheral pulses, although very weak femoral pulsation the result of collateral circulation may occasionally be felt. A cool and pale foot, dependent rubor, a decreased or reduced oscillometric recording in the thigh and calf, and the conclusive evidence of obstruction seen in an aortogram usually suffice to make the diagnosis of arterial occlusive disease. A very useful table, with the main diagnostic differences between vascular, neurologic and musculoskeletal lesions is presented. Differential diagnosis of the low back, thigh, or gluteal pain should include consideration of arterial occlusion or insufficiency.

KITCHELL

Moser, M., Babin, S. M., Cotts, W., and Prandoni, A. G.: Acute Massive Venous Occlusion: Report of a Case Successfully Treated With Exercise. Ann. Int. Med. **40:** 361 (Feb.), 1954.

Because of the marked difference in therapy in acute massive venous occlusion as opposed to acute arterial occlusion, it is extremely important to make a correct diagnosis. This may be especially difficult in elderly patients, because there may be coincidental obliterative arterial disease at the time of the venous occlusion. Peripheral pulses may be absent and yet not be associated with acute arterial blockage. Extreme difficulty in making the differential diagnosis may also be encountered because of a rather sudden vasoconstriction of the arterial vessels as well as the venous channels following an acute venous occlusion. This, too, may cause the peripheral pulses to be feeble or the oscillometric indexes to be reduced. In arterial occlusion, these latter findings are, of course, more pronounced. There are two clinical signs of acute massive venous occlusion which should definitely suggest the diagnosis: (a) intense bluish-purple (cyanotic) discoloration of the extremity distal to the area of occlusion; and (b) marked edema and "turgidity" of the extremity. This often develops within a matter of minutes or hours. In contrast to this, in acute arterial occlusion the extremity is waxy or yellow-white and usually not markedly edematous. A case of acute massive venous occlusion of a lower extremity is presented. This apparently resulted from extension of a previous thrombophlebitis. Immediate treatment with elevation and continuous exercise of the extremity was employed, with excellent results. This treatment would appear to be the logical one to employ, since the major pathology in the condition results from "complete blockage" of venous outflow from the extremity. Efforts to promote this "outflow" should be made immediately. Chemical sympathetic blocking procedures (oral dibenzyline and parenteral hexamethonium) were employed after exercise had been instituted. The use of drugs to produce release of reflex vasoconstriction would appear to present a definite advantage over the use of surgical procedures, especially in a patient who is on anticoagulant therapy.

WENDKOS

German, W. J., and Black, S. P. W.: Experimental Production of Carotid Aneurysms. New England J. Med. **250:** 104 (Jan. 21), 1954.

The authors describe a technic for the experimental production of aneurysms of the carotid artery in dogs using a vein-pouch graft from the external jugular vein. Five aneurysms were produced by this method. The evidence of patency of the aneurysms consisted of an audible bruit, visible and palpable pulsation on re-exposure of the aneurysms and serial arteriography. One aneurysm, still patent after five months, showed an increase in volume from 304 to 460 cu. mm. in 15 weeks. There is apparently a critical size of aneurysm below which patency is lost. Preliminary studies of hemodynamics of these experimental "berry" aneurysms disclosed, in a week-old aneurysm, a decrease in systolic thrust in the parent artery cephalad to the aneurysm, compared to that in the caudad portion of the artery. This was felt to suggest a relative depulsator action of the aneurysm upon the systolic thrust in the distal portion of the artery. This effect was not demonstrable when the aneurysm was five months old. Cinefluorographic observations of the

hemodynamic cycle within the aneurysms indicated that the flow into the aneurysm appeared in the form of a jet. Complete opacification of the aneurysm did not appear immediately but a swirling motion of the opacified fluid indicated a turbulent flow within the aneurysm. Deopacification of the aneurysm occurred at a relatively slow rate.

ROSENBAUM

Balfour, D. C., Jr., Reynolds, T. B., Levinson, D. C., Mikkelsen, W. P., and Pattison, A. C.: Hepatic Vein Pressure Studies for Evaluation of Intrahepatic Portal Hypertension. Arch. Surg. **68:** 442 (Apr.), 1954.

The authors used the "wedge" pressure in the hepatic vein as a means of preoperative evaluation of portal hypertension. In order to obtain the readings, they introduced a nylon catheter into an arm vein and passed it through the right auricle and inferior vena cava into the hepatic vein. The catheter tip was then wedged into a radicle of the latter vessel. Pressures were determined by means of a strain gage. No ill effects were noted from the procedure.

The study was carried out on 10 patients preoperatively, while in six the pressure was followed throughout portacaval surgical procedures. In some instances simultaneous portal vein pressures were obtained. It was noted that the wedge pressure in the hepatic vein averaged 4 or 5 mm. Hg less than the actual pressure in the portal vein. The procedure demonstrated that hepatic artery ligation did not lower portal hypertension.

ABRAMSON

Brown, R. B., Hufnagel, C. A., Pate, J. W., and Strong, W. R.: Freeze-dried Arterial Homografts; Clinical Application. Surg., Gynec. & Obst. **97:** 657 (Dec.), 1953.

The authors utilized freeze-dried arterial homografts in the surgical treatment of aneurysms of major vessels, including the aorta, of coarctation of the aorta, and of segmental occlusive diseases of major vessels. The type of homografts used appeared to have certain advantages over those which employ a quick freezing technic with storage at −80 C. and also over those which utilize a tissue culture-like medium, with storage at 1 to 3 C. They were obtained at sterile autopsies and were removed within 24 hours after death, the body having been refrigerated in the interim. The vessel segments were placed in glass tubes and frozen by immersion in a mixture of absolute alcohol and dry ice at −78 C. Then they were placed either directly into a freeze-drying machine or into storage at dry-ice temperature to await freeze-drying. For the latter, a modified commercial freeze-drying machine was used.

Of the seven patients treated with the above type of homograft, patency of the graft was maintained in all instances during the period of observation (one to nine months).

ABRAMSON

Wilens, S. L., and McCluskey, R. T.: The Permeability of Excised Arteries and Other Tissues to Serum Lipid. Circulation Research **2:** 175 (Mar.), 1954.

The permeability of excised tissues was measured by filtration of blood serum under pressure. Arteries, ureters and small intestines were only slightly permeable to serum lipids and proteins; veins and appendices permitted passage of a large proportion of these materials.

The permeability of excised arteries differed from that of other tissues in that the rate of filtration was much slower and in that after prolonged filtration lipid was deposited intramurally in zonal accumulations at the internal and external elastic lamellae. The excised artery was equally impermeable to serum cholesterol, phospholipid and total lipid. The rate of filtration and the amount of lipid deposited were reduced in the thicker arteries of older individuals in contrast to arteries of young and middle-aged adults.

MAXWELL

Ecker, A.: Emotional Stress before Strokes: A Preliminary Report of 20 Cases. Ann. Int. Med. **40:** 49 (Jan.), 1954.

The author reports that preceding a cerebral stroke patients have often suffered long-standing progressive difficulty in settling emotional problems. They may have faced overwhelming personal threat. Such life situations, in which the stroke occurs, have usually been overlooked, perhaps because the physician has been absorbed in the physical features of the case. Except for the occasional reference to anger immediately preceding apoplexy, medical literature has generally been silent about the association of stroke and previous emotion.

The purpose of this report is to present a series of 20 cases illustrating the association between cerebral accidents and preceding emotional stress. It is not claimed that such emotional settings are the only factors implicated in cerebral strokes, but they may prove to be contributory. In 13 of these cases, there were long standing personality difficulties preceding the stroke, and in 15 there was a special emotional stress which immediately preceded the strokes; in eight cases both factors were present. Angiograms technically suitable for study of spasm of the cerebral arteries were available in 15 cases. In all of these there was an excessive tendency to arterial contraction. This spastic tendency may be one of the bodily expressions of the emotional disturbance. Ischemia resulting from excessive arterial contraction doubtless contributes to the pathologic changes in the brain and its blood vessels. The author feels that

the high incidence of major emotional problems preceding intracerebral vascular accidents warrants further attention.

DENNISON

OTHER SUBJECTS

Hahn, R. S., Holman, E., and Frerichs, J. B.: Role of the Bronchial Circulation in the Etiology of Pulmonary and Pericardial Suppuration. J. Thoracic Surg. **27:** 121 (Feb.), 1954.

An experimental study was performed on dogs in order to evaluate the role of the bronchial artery as a route for hematogenic infection of the lung and pericardium. The injection of small particles of infected blood clot into the right posterior brachial artery resulted uniformly in failure to produce pulmonary suppuration or abscess. In contrast, there was a high incidence of suppurative lesions of mediastinal organs, pleurae, chest wall, heart and pericardium. Such findings suggested that the bronchial artery was more important as a mediator of infection to these structures than to the bronchopulmonary organs with which this vascular system is usually associated.

ABRAMSON

BACTERIAL ENDOCARDITIS

Wood, W. S., and Hall, B.: Rupture of Spleen in Subacute Bacterial Endocarditis. Arch. Int. Med. **93:** 633 (Apr.), 1954.

A case is presented of subacute bacterial endocarditis and rupture of the spleen in a patient who recovered. Left upper quadrant pain and tenderness were prominent findings at the time of admission and splenic infarcts were suspected. On the sixth day of antibiotic therapy, the patient suddenly displayed the symptoms and signs of massive intraperitoneal hemorrhage. At operation, rupture of a mycotic aneurysm of the splenic artery was found. This is apparently the first reported case of a rupture of the splenic artery associated with rupture of the spleen, and the twelfth reported case of rupture of the spleen secondary to bacterial endocarditis.

BERNSTEIN

Newman, W., Torres, J. M., and Guck, J. K.: Bacterial Endocarditis. An Analysis of Fifty-two Cases. Am. J. Med. **16:** 535 (Apr.), 1954.

Murmurs, fever, anemia and positive blood cultures were the major clinical manifestations of bacterial endocarditis in 52 cases collected over a six and one-half year period. Congestive heart failure occurred early in the course of the disease in 25 per cent of the patients, while auricular fibrillation occurred early in 15 per cent, so that these conditions should not be considered rare findings in bacterial endocarditis. The degree of pre-existing valvular deformity appears to be an important factor in the appearance of congestive heart failure during bacterial endocarditis. Although congestive heart failure had no effect on the bacteriologic cure rate, it had an adverse effect on the mortality rate (74 per cent) in adequately treated patients. The cured-infection rate in adequately treated patients was 69 per cent. Of the 27 patients cured of their infection, one-third died from sequelae of the disease; one-third are alive but disabled; and one-third are alive and asymptomatic. Since the authors believe the duration of the disease is an important factor in the development of embolization and congestive heart failure in bacterial endocarditis, they feel that early diagnosis and treatment are of paramount importance. Of practical value and of great interest was the observation that when a positive blood culture was obtained, it appeared in at least one of the first four cultures taken. Positive blood cultures were found in three patients who were afebrile. Bacteriologic cure of bacterial endocarditis seemed to have a beneficial effect on the renal lesions capable of producing renal insufficiency in this group of cases.

HARRIS

BLOOD COAGULATION

Havel, R. J., and Boyle, E.: Production of Lipemia Clearing Factor During Anaphylactoid Shock. Proc. Soc. Exp. Biol. & Med **85:** 468 (Mar.), 1954.

Anaphylactoid shock was produced in 12 of 13 mongrel dogs under anesthesia by either Peptone solution or histamine liberators given intravenously. Determinations were made of clotting time before and during shock and after an antiheparin agent (protamine) was given. Clearing factor analyses were done on the same blood samples by measuring the decrease in optical density of the chylons layer of lipemic human plasma. In nine dogs, clotting time was prolonged and in all of these there was evidence of production of clearing factor. In three other animals where shock was produced there was no prolongation of clotting time, but clearing factor was produced. The amount of clearing factor produced by submitting the dogs to shock was considerably less than that produced in normal dogs by heparin injection causing the same prolongation of clotting time. This was shown experimentally to be a function of the shocked state. The clearing factor produced was shown to be identical to that produced by heparin injection. Antiheparin agents decreased clotting time and abolished clearing factor substance from the blood in all seven of the animals to which it was given.

HARVEY

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

1955 HEART FUND CAMPAIGN

For the seventh consecutive year, the month of February will be devoted to the annual Heart Fund campaign conducted by the Association and its affiliates. The goal of the drive will be the raising of funds to support a year-round program of scientific research, professional and lay education and community service efforts. Last year's Heart Fund receipts totalled $11,330,195.47.

Most of the monies raised by the Heart Fund are retained by the affiliated Heart Associations to maintain local programs. More than half of the 25% allotted to the National Office is devoted to the support of scientific research on a nationwide basis. Much of the research is of a fundamental nature. A great deal of it also is aimed at discovering the causes of atherosclerosis, rheumatic fever and high blood pressure, and at finding ways to improve the methods of treatment and control of cardiovascular diseases.

For the second successive year, General Mark W. Clark, now President of The Citadel, a military college in Charleston, S. C., will serve as National Campaign Chairman of the Heart Fund. The campaign slogan will once again be "Help Your Heart Fund—Help Your Heart."

February 20 has been designated as Heart Sunday. On that date, several hundred communities will hold a concentrated house-to-house collection.

As in the past campaigns, the medical profession may be counted upon to make valuable contributions to the success of the Heart Fund drive. Because development of necessary public understanding of the nature of cardiovascular diseases would be impossible without the active participation of physicians, they will serve as speakers and committee members, thus informing the public on the progress being made in research and in the treatment and care of heart patients, and on how public contributions to the Heart Fund will accelerate that progress.

NOMENCLATURE SHEETS

Two separate nomenclature sheets, one for *Diagnosis of Diseases of the Heart* and one for *Diagnosis of Peripheral Vascular Diseases*, are now available through the Association.

The 11″ by 17″ sheets are intended for the use of cardiologists, internists, family physicians, medical students, interns, residents, hospitals, clinics and health departments. They serve as a handy check list and as a guide to systematic recording of diagnoses. Both nomenclature sheets (Diseases of the Heart, and Peripheral Vascular Diseases) may be obtained in either coded or uncoded form. The coded nomenclature carries the code numbers of Standard Nomenclature of Diseases and Operations sponsored by the AMA, and should be requested for the use of hospitals and clinics.

The authoritative source for both nomenclature sheets is the monograph, "Nomenclature and Criteria for Diagnosis of the Diseases of the Heart and Blood Vessels" (Fifth Edition—1953), published by the New York Heart Association.

The price of either Nomenclature Sheets for Diagnosis of Diseases of the Heart or Nomenclature Sheets for Diagnosis of Peripheral Vascular Diseases is $.70 per hundred, either coded or uncoded. They may be ordered either from the American Heart Association, 44 East 23 Street, New York 10, N. Y., or from your local Heart Association.

CINE-ANGIOCARDIOGRAMS

A series of "Cine-Angiocardiograms for Teaching" is now available for use in instructing medical students, interns, residents, nurses, physicians attending post-graduate courses and other groups. These cine-angiocardiograms are presented in a set of 17 loops.

Each loop is designed to illustrate one specific point of information. Fourteen of the loops show congenital cardiovascular anomalies; one shows an acquired aortic aneurysm; the remaining two illustrate normal hearts. A concise descriptive outline of all of the loops may be obtained from your local Heart Association or from the American Heart Association.

Because of the loop form, the instructor can maintain any subject on the screen as long as required. The cine-angiocardiograms can be projected continuously on any 16 mm. silent projector or on a 16 mm. sound projector which has provision for showing silent films.

The cine-angiocardiograms were developed by James S. Watson, M.D., and can be purchased directly from Dr. Watson at the University of Rochester, Rochester, N. Y. They may also be rented from the AHA Film Library, 13 East 37 Street, New York 16, N. Y. Rental rates are: $3.50 for one day; $5.00 for two days; $8.00 for five days. Information on the special adaptation of the cine-angiocardiograms for television use is available from Dr. Watson.

SECOND WORLD CONGRESS OF CARDIOLOGY PROGRAMS

Copies of Part II of the printed program for the Second World Congress of Cardiology may be obtained at the reduced price of $1.50 each from the American Heart Association, 44 East 23 Street, New York 10, N. Y. The 559-page volume contains abstracts of close to 350 papers presented at the formal scientific sessions. The abstracts are printed in English, with translations in Interlingua, a new international language, and in some cases, in their original language.

COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

Eugene B. Ferris, M.D., Professor of Medicine at Emory University in Atlanta, Ga., was elected Chairman of the Medical Advisory Board of the Council for High Blood Pressure Research of the American Heart Association during the Council's meeting in Cleveland, October 22–24. Thomas Findley, M.D. was named Vice Chairman. Dr. Findley was recently appointed to the Chair of Cardiovascular Research established by the Georgia Heart Association at the Georgia College of Medicine in Augusta.

The Council named Maynard Hale Murch of Cleveland as its President. Mr. Murch, president of the investment banking firm which bears his name, succeeds Adrian Joyce who died on August 24.

HEART ASSOCIATION APPOINTS ASSISTANT MEDICAL DIRECTOR

Robert S. Warner, M.D., has joined the professional staff of the American Heart Association as an Assistant Medical Director. Dr. Warner was formerly Director of the Division of Graduate and Post-Graduate Medical Education at the University of Utah College of Medicine. He will be concerned primarily with the development of the Association's professional medical education program. Dr. Warner also served as an Instructor in Preventive Medicine at the Utah College of Medicine.

Charles D. Marple, M.D., Association Medical Director, also announced the appointment of an Administrator for the Medical Division. He is Carmine Mangano, M.S.S.W., formerly Executive Director of Irvington House, Irvington-on-Hudson, N. Y., a research and treatment center for children with rheumatic fever.

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

The American Society for the Study of Arteriosclerosis has announced the election of Louis N. Katz, M.D. of Chicago as President for 1955. Dr. Katz is Director of the Cardiovascular Department of the Medical Research Institute at Michael Reese Hospital. Other officers named were: Vice President—Arthur C. Corcoran, M.D., Cleveland. Secretary-Treasurer—O. J. Pollak, M.D., Dover, Delaware.

The Society will hold its 1955 meeting at the Hotel Sheraton in Chicago on November 6 and 7. Charles Fore Wilkinson, Jr., M.D. of New York will serve as Program Chairman. The deadline for submission of factual abstracts of unpublished work to be presented at the meeting is May 31.

CARDIOVASCULAR SURGERY SYMPOSIUM

An International Symposium on Cardiovascular Surgery will be held under the auspices of the Henry Ford Hospital in Detroit, March 17–19. The symposium will deal with "recent studies in physiology, diagnosis and technics." Inquiries should be addressed to the Secretary, International Symposium on Cardiovascular Surgery, Henry Ford Hospital, Detroit 2, Michigan.

ELECTROCARDIOGRAPHIC INTERPRETATION COURSE

A 12-week course in Electrocardiographic Interpretation for graduate physicians will be conducted at the Michael Reese Hospital in Chicago beginning February 2. The course will be directed by Louis N. Katz, M.D., Director of the Cardiovascular Department of the Medical Research Institute. Further information may be obtained from Mrs. Ana Rose, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

JAPANESE PHYSICIANS SEEK MEDICAL PHOTOS

A request has been received from the Japan Medical Association for photographs illustrating medical and research work, medical teaching facilities, hospitals and the functioning of ancillary services in the United States and Canada. These pictures are to be used for a "World Exhibition in Medical Sciences" to be presented in conjunction with the 14th Congress of the Japanese medical group to be held in Kyoto, Japan, from April 1–5. Photos must be sent by January 31 to: Director, Exhibition Department, Department of Pharmacology, Faculty of Medicine, Kyoto University, Kyoto, Japan.

AHA ANNUAL MEETING SCHEDULED FOR FALL, 1955

The Association's Annual Meeting and Scientific Sessions have been scheduled for the Fall this year, instead of the Spring as in past years. The meeting is tentatively set for October 22–27 at the Jung Hotel in New Orleans.

MEETINGS CALENDAR

Jan. 28–29: Western Society for Clinical Research, Carmel, Calif. Herbert N. Hultgren, Stanford Hospital, San Francisco 15.

Feb. 9–12: Society of University Surgeons, Houston, Tex. 1325 S. Grand Blvd., St. Louis 4.

Feb. 17–19: Central Surgical Association, Chicago. Robert M. Zollinger, University Hospital, Columbus 10, Ohio.

March 16–19: Neurosurgical Society of America, Pebble Beach, Calif. Lester A. Mount, 700 West 168 Street, New York 32, N. Y.

March 17–19: International Symposium on Cardiovascular Surgery, Henry Ford Hospital, Detroit. Dr. Conrad R. Lam, 2799 West Grand Blvd., Detroit 2.

April 10–16: American Society of Experimental Pathology, San Francisco. Cyrus C. Erickson, 874 Union Ave., Memphis 3.

April 10–16: American Society for Pharmacology and Experimental Therapeutics, San Francisco. Carl C. Pfeiffer, 1853 W. Polk Street, Chicago 12.

April 23–29: Industrial Medical Association, Buffalo, N. Y. H. Glenn Gardiner, Inland Steel Co., East Chicago, Ind.

April 24–29: Inter-American Congress of Radiology, Shoreham Hotel, Washington, D. C. Dr. Eugene P. Pendergrass, 3400 Spruce Street, Philadelphia 4.

April 27–29: American Surgical Association, Philadelphia. R. Kennedy Gilchrist, 59 E. Madison Street, Chicago 3.

ABROAD

Lima, Peru: Pan-American Academy of General Practice, Feb. 11–25. Dr. Arturo, Martinez, 54 East 72nd Street, New York 21, N. Y.

Lima, Peru: Latin American Congress of Physical Medicine, Feb. 14–19. Dr. Cassius Lopez de Victoria, 176 East 71 Street, New York 21, N. Y.

Kyoto, Japan: Japan Medical Association—14th Congress, April 1–5. Dr. Mitsuhary Goto, University Hospital, Medical Faculty of Kyoto University, Kyoto, Japan.

Beirut, Lebanon: Middle East Medical Assembly, April 22–24. Dr. John L. Wilson, American University of Beirut, Beirut, Lebanon.

INDIANA UNIVERSITY HEART SYMPOSIUM

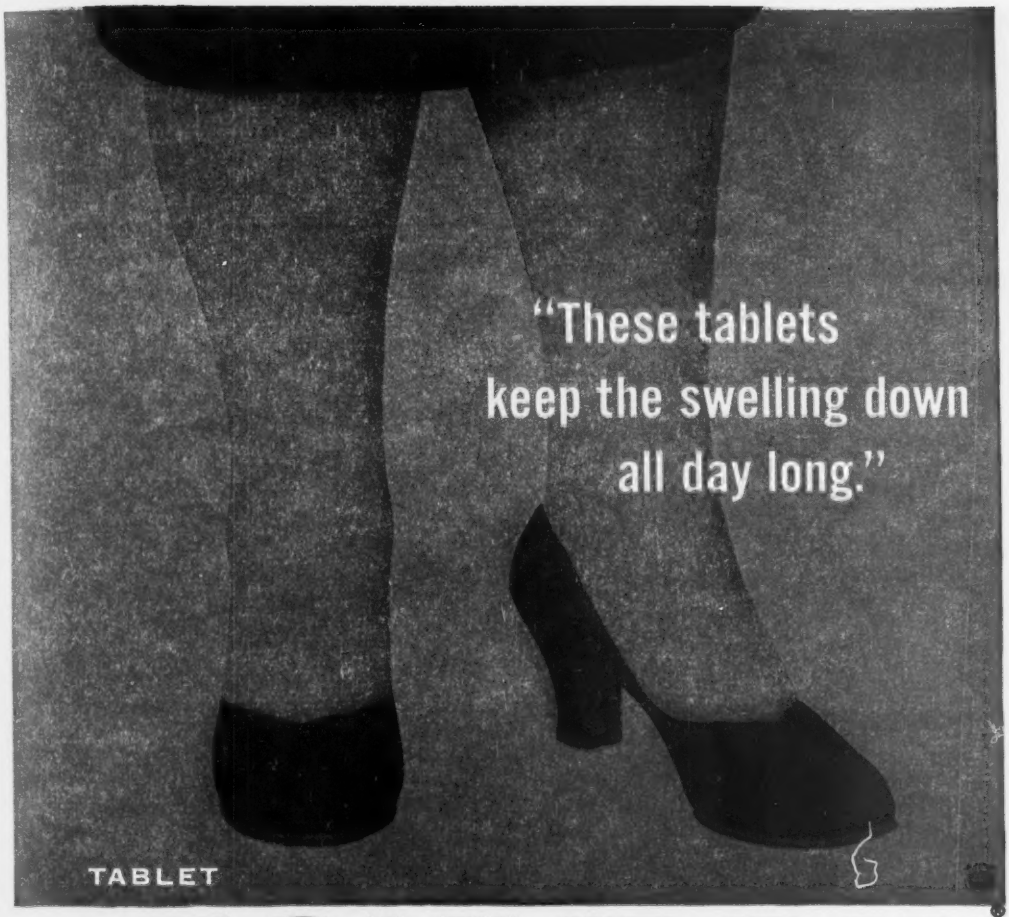
The fourth annual heart symposium, cosponsored by the Indiana Heart Foundation and the University of Indiana School of Medicine, is scheduled for Thursday, January 20, at the School of Medicine auditorium in Indianapolis. The program includes clinical conferences and a panel discussion on "The Heart in Rheumatic Fever." Among those invited to participate are Drs. Robert H. Bayley, Oklahoma City; Howard B. Burchell, Rochester, Minn.; Charles A. R. Connor, New York; A. C. Corocran, Cleveland; John C. Jones, Los Angeles; Ancel Keys, Minneapolis; Charles Rammelkamp, Cleveland; Jefferson M. Crimson, Stanford, Calif.; Harold Green, Winston-Salem; Howard B. Sprague, Brookline, Mass.; Francis C. Wood, Philadelphia; and Harland G. Wood, Cleveland, all members of the Research Committee of the American Heart Association.

SUMMARIES IN INTERLINGUA

Beginning with this issue, summaries of articles appearing in CIRCULATION will be published regularly in the new international scientific language, Interlingua, as well as in English.

This change was instituted at the urging of many CIRCULATION readers, particularly those abroad. They expressed the belief that presentation of the summaries in Interlingua, which is constructed from components common to Spanish, Portuguese, French, Italian and other Romance languages, would increase the worth of CIRCULATION as a journal of cardiologic information with an international readership.

The existence and value of Interlingua were first made known to many in the cardiovascular field at the time of the Second World Congress of Cardiology held in Washington last September. Abstracts of papers presented at the Congress were published in the program in Interlingua. Largely spurred by the employment of the international language at the Congress, there are now nine United States scientific publications, including CIRCULATION and BLOOD, also published by Grune and Stratton, utilizing Interlingua as a secondary editorial language. One Peruvian and several European journals employ Interlingua in this same way. In addition, two scientific journals published in this country are printed in Interlingua exclusively.



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